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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3173/2:

TUMOR PROMOTION AND COCARCINOGENESIS IN MOUSE SKIN

1. INITIATION AND PROMOTION AT DIFFERENT AGES AND DOSES IN 2200 MICE. I. METHODS, AND THE APPARENT PERSISTENCE OF INITIATED CELLS.

Stenback F, Peto R, Shubik P
Dept. Pathology, Univ. Oulu, SF 90220, Oulu 22, Finland
Br J Cancer; 44(1):1-14 1981

Delay between initiation and promotion on mouse skin was in 1949 reported by Berenblum and Shubik not to affect tumor yields, and this led to the important concept of the irreversibility of initiation and stimulated the development of multistage models. Subsequent reports have, however, suggested that delay does decrease tumor yields, and this is confirmed by the present study of 2,200 mice initiated at 8, 48, or 68 wk with 10, 30, 100, or 300 ug of DMBA and promoted by a standard dose of TPA for 15 wk, after various delays. However, our data suggest that the decrease in tumor yields is chiefly or wholly due to a reduction, among ageing mice, of the ability to respond to promoters, and not to any substantial loss of initiated cells, for late initiation with immediate promotion also yielded a less rapid response than early initiation with immediate promotion. Interpretation of all such studies is complicated by the few wk that the skin needs to repair ulceration and other damage induced by the higher doses of DMBA, for if promotion with TPA begins before such repair is complete the tumor yield may be misleadingly increased. (Author abstract) (25 Refs)

2. INITIATION AND PROMOTION AT DIFFERENT AGES AND DOSES IN 2200 MICE. II. DECREASE IN PROMOTION BY TPA WITH AGEING.

Stenback F, Peto R, Shubik P
Dept. Pathology, Univ. Oulu, SF 90220, Oulu 22, Finland
Br J Cancer; 44(1):15-23 1981

Using the data described in Paper I, we compare the effects of the same treatment timings and doses given at different ages. Initiation with DMBA at 68 wk of age, followed 3 wk later by TPA, has a significantly (p less than 0.0001) less rapid effect on subsequent tumor incidence than does initiation at 8 or at 48 wk of age, followed 3 wk later by TPA. We suggest that this is chiefly due not to changes in the numbers of cells initiated by DMBA, but rather to a decrease in the promotional efficacy of TPA in ageing mice. (Author abstract) (10 Refs)

3. INITIATION AND PROMOTION AT DIFFERENT AGES AND DOSES IN 2200 MICE. III. LINEAR EXTRAPOLATION FROM HIGH DOSES MAY UNDERESTIMATE LOW-DOSE TUMOUR RISKS.

Stenback F, Peto R, Shubik P
Dept. Pathology, Univ. Oulu, SF 90220, Oulu 22, Finland
Br J Cancer; 44(1):24-34 1981

The dose-response relationships from the data described in Paper I were analyzed. Among unpromoted animals, only doses sufficient to cause ulceration with subsequent promotion due to wound healing caused a rapid crop of tumors, so the dose-response curve exhibited strong upward curvature. Among promoted animals, the response of the skin to initiation appeared to have been nearly saturated by all dimethylbenzanthracene (DMBA) doses tested, so that a 30-fold decrease in dose produced only a 3-fold decrease in effect. The dose-response relationship thus exhibited strong downward curvature. Among promoted animals, estimation of the risks associated with very low doses of carcinogen by linear extrapolation through the origin from the effects of larger doses (which is often assumed to be conservative) would underestimate the true risks by 10-fold or more. Our results emphasize that whereas linear interpolation from the results of high doses may be reasonable for data on the effects of continuous treatment with non-toxic dose l evels of carcinogen, it may be misleading when extrapolating, as here, from the effects of single large doses. (Author abstract) (18 Refs)

4. SKIN TUMOR-PROMOTING ACTIVITY OF BENZOYL PEROXIDE, A WIDELY USED FREE RADICAL-GENERATING COMPOUND.

Slaga TJ, Klein-Szanto AJ, Triplett LL, Yotti LP, Trosko JE
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Science; 213(4511):1023-1025 1981

Benzoyl peroxide, a widely used free radical-generating compound, promoted both papillomas and carcinomas when it was topically applied to mice after 7,12-dimethylbenz[a]anthracene initiation. Benzoyl peroxide was inactive on the skin as a complete carcinogen or as a tumor initiator. A single topical application of benzoyl peroxide produced a marked epidermal hyperplasia and induced a large number of dark basal keratinocytes, effects similar to those produced by the potent tumor promoter 12-O-tetradecanoyl phorbol-13-acetate. Benzoyl peroxide, like other known tumor promoters, also inhibited metabolic cooperation (intercellular communication) in Chinese hamster cells. In view of these results caution should be recommended in the use of this and other free radical-generating compounds. (Author abstract) (24 Refs)

5. THE NATURE OF THE EPIDERMAL GROWTH PRODUCED BY THE FIRST APPLICATION OF 12-O-TETRADECANOYL-PHORBOL-13-ACETATE ON THE SKIN OF MICE INITIATED WITH DIMETHYLBENZANTHRACENE.

Argyris TS
Dept. Pathology, State Univ. New York, Upstate Medical Center, Syracuse, NY, 13210
J Invest Dermatol; 77(2):230-234 1981

We have investigated the kinetics of epidermal growth following a single application of 17 nmoles of 12-O-tetradecanoyl-phorbol-13-acetate (TPA) in the back skin of CD-1 female mice initiated with 200 nmoles of dimethylbenzanthracene (DMBA). Within 5 hr after the application of TPA there is an increase in epidermal wet wt and total protein (protein/unit area of epidermis) which reached their peak of 3 to 4x that of normal between 3 and 4 days. Total DNA reaches its peak of about 2x increase above normal by day 2. All these parameters remain elevated until 7 days after TPA treatment when they begin to return toward normal levels. But, by day 10, the end of the experimental period, they are still significantly elevated above normal levels. The principal hyperplasia appears with marked increases in the number of nucleated cell layers, the total number of nuclei/mm interfollicular epidermis (IFE) and the number of suprabasal nuclei/mm IFE which by day 2 reach their peak of about 2-3x normal; one sees considerable epidermal cell damage as evidenced by cytoplasmic vacuolization, nuclear pyknosis, and the separation of the epidermis from the dermis. This period of damage is associated with a decrease in the number of basal nuclei/mm IFE. A comparison of the epidermal growth produced by the first application of

TPA in initiated mouse skin with that in normal mouse skin, suggests that the overall growth produced by the first application of TPA in initiated mouse skin is of greater duration than that produced by TPA in normal mouse skin. (24 Refs)

6. EFFECTS OF THE TUMOR PROMOTER 12-O-TETRADECANOYL-PHORBOL-13-ACETATE ON NEWLY SYNTHESIZED PROTEINS IN MOUSE EPIDERMIS.

Laskin JD, Mufson RA, Piccinini L, Engelhardt DL, Weinstein IB

Div. Environmental Sciences Cancer Center/Inst. Cancer Res., Coll. Physicians and Surgeons, Columbia Univ., 701 West 168th St., New York, NY, 10032

Cell; 25(2):441-449 1981

We have analyzed the effects of treatment of mouse epidermis with the potent tumor promoter 12-O-tetradecanoyl-phorbol-13-acetate on the profile of newly synthesized proteins. TPA was applied to the skin of the intact mouse, and either 3 or 24 hr later skin fragments were pulse-labeled in vitro with 35S-methionine for 4 hr. The epidermal proteins were extracted and separated by two-dimensional gel electrophoresis. Over 200 individual proteins were resolved in acidic gels. At least 10 of these showed major (by a factor of 5 or more) increases or decreases in response to TPA; 8 of these appear to be keratin proteins. Two-dimensional gel profiles of basic proteins synthesized by mouse epidermis resolved over 100 individual proteins. Only one of these showed a significant change in response to TPA. This 41 kd protein increased more than 100-fold within 24 hr after the application of TPA. Treatment of mouse skin with mezerein, a plant diterpene structurally related to TPA, produces an almost identical change in the pattern of proteins produced. Four agents that induce hyperplasia but are not potent tumor promoters, ethylphenylpropiolate, acetic acid, turpentine oil and the Ca++ ionophore A23187, modulate the synthesis of only three of the keratin proteins. Thus the changes in protein profiles induced by TPA and mezerein are not simply the consequence of hyperplasia. In addition, application to mouse skin of a glucocorticoid that is a potent inhibitor of tumor promotion inhibits most of the changes in protein profiles induced by TPA. Taken together, these results indicate that TPA and mezerein induce early and marked changes in the profile of specific epidermal proteins. It seems likely that some of these changes are directly related to the process of tumor promotion. (Author abstract) (39 Refs)

7. LACK OF ENHANCEMENT OF EXPERIMENTAL PHOTOCARCINOGENESIS BY TOPICAL RETINOIC ACID.

Kligman LH, Kligman AM

Duhring Lab., Dept. Dermatology, Univ. Pennsylvania Sch. Medicine, 36th and Hamilton Walk, Philadelphia, PA

Arch Dermatol Res; 270(4):453-462 1981

The ability of retinoic acid (RA) to enhance UV carcinogenesis was studied in lightly pigmented hairless mice. In the first series of the experiments, animals were subjected to 30-wk UV irradiation and concomitant topical administration of RA followed by 15-wk RA administration. In the second series of the experiments, animals received UV irradiations alone for the first 30 wk and then RA alone for the next 15 wk. UV irradiation induced multiple skin papillomas in 100% of the animals. RA administration (either concomitantly with UV or after tumor induction) did not affect the latent period, tumor yield or tumor progression. (39 Refs)

8. THE INFLUENCE OF RETINOIDS ON POLYAMINE AND DNA SYNTHESIS IN MOUSE EPIDERMIS.

Boutwell RK, Verma AK

McArdle Lab. for Cancer Res., Univ. Wisconsin, Madison, WI, 53706

Ann NY Acad Sci; 359:275-280 1981

The effect of retinoic acid (RA) on skin carcinogenesis in mice was studied. RA did not affect the yield of skin papillomas induced by repeated applications of dimethylbenzanthracene (DMBA). RA application in initiation-promotion protocol (single DMBA application at a dose that does not produce tumors followed by repeated applications of the promoter 12-O-tetradecanoylphorbol-13-acetate: TPA) inhibited the yield of skin papillomas. RA did not inhibit the induction in epidermis of ornithine decarboxylase (ODC) by DMBA, but reduced markedly induction of ODC by TPA. RA pretreatment enhanced initial depression of DNA synthesis in mouse skin by TPA. RA pretreatment did not change DNA synthesis following a carcinogenic dose of DMBA. (24 Refs)

9. INTRACELLULAR CALCIUM AND SKIN TUMOR PROMOTION: CALCIUM REGULATION OF THE INDUCTION OF EPIDERMAL ORNITHINE DECARBOXYLASE ACTIVITY BY THE TUMOR PROMOTER 12-O-TETRADECANOYLPHORBOL-13-ACETATE.

Verma AK, Boutwell RK

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Biochem Biophys Res Commun; 101(2):375-383 1981

The role of calcium as an intracellular second messenger for ornithine decarboxylase (ODC) induction by 12-O-tetradecanoylphorbol-13-acetate (TPA) was studied in skin explants of female Charles River CD-1 mice. Addition of 2.15 uM TPA to a serum-free medium, which contained 1.82 milliM (mM) Ca++ and 0.83 mM Mg++, resulted in about a 200-fold increase in ODC activity. The peak activity occurred at about 8 hr. ODC activity returned to near basal levels at about 18 hr. Addition of 1.2 mM ethyleneglycol-bis-(beta-aminoethyl ether) N,N'-tetraacetic acid (EGTA), a calcium chelating agent, did not prevent ODC induction, whereas 3.6 mM EGTA resulted in an 85% inhibition of ODC induction by TPA. Inhibition of ODC induction by EGTA was overcome by restoration of extracellular calcium (but not magnesium) in the medium. Incubation of mouse skin pieces in the presence of 10 uM trifluoperzine (TFP), a calmodulin inhibitor, did not affect ODC induction by 5 uM TPA. However, addition of 50 and 100 uM TFP resulted in 27% and 60% inhibition of ODC induction, respectively. Lanthanum chloride (0.1 mM), which antagonizes the effects of calcium possibly by displacing surface-bound calcium as well as by blocking calcium influx, did not inhibit ODC induction by 5 uM TPA, whereas a 71% inhibition was observed at 5 mM lanthanum chloride. The results suggested that calcium may be an intracellular second messenger for ODC induction by TPA. (24 Refs)

TUMOR PROMOTION AND COCARCINOGENESIS IN OTHER ANIMAL MODELS

10. EFFECT OF PHENOBARBITAL ON THE DEVELOPMENT OF NEOPLASTIC LESIONS IN THE LIVER OF CYCASIN-TREATED RATS.

Uchida E, Hirono I
Second Dept. Pathology, Nippon Medical Sch., Sendagi, 1-1-5, Bunkyo-ku, Tokyo 113, Japan
J Cancer Res Clin Oncol; 100(3):231-238 1981

The effect of phenobarbital (PHE) on neoplastic lesions induced in the liver and kidney of ACI rats by a single administration of cycasin (CYC) was investigated. Rats were placed into one of four groups: Group 1 received 100 mg CYC/kg by gavage and PHE at a level of 0.05% in their diet until the termination of the experiment; Group 2 received CYC alone; Group 3 received PHE alone; and Group 4 received no treatment. In Group 1, liver tumors were induced in 1/12 males and 7/12 females and one sarcoma and one interstitial tumor of the kidney were also induced. In Group 2, one liver tumor was found in a female, and two interstitial tumors of the kidney and one jejunal adenocarcinoma were induced. In Group 3, only one interstitial cell tumor in the testis was found. In Group 4, two interstitial cell tumors in the testes, one pituitary adenoma, and one adrenocortical adenoma were found in males, and one pancreatic exocrine adenoma was found in a female. Significant numbers of gamma-glutamyl-transpeptidase (GGT)-positive foci were induced in Groups 1 and 3. In Group 2, a small number of tiny foci were seen. Many GGT-positive foci were observed in Group 4, however, they were small-sized. Thus, PHE possesses a tumor-promoting effect in terms of induction of neoplastic lesions in the liver, but not the kidney. (27 Refs)

11. PROMOTIVE EFFECTS OF DEOXYCHOLIC ACID ON HEPATOCARCINOGENESIS INITIATED BY DIETHYLNITROSAMINE IN MALE RATS.

Cameron R, Imaida K, Ito N
First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan
Gan; 72(4):635-636 1981

The ability of deoxycholic acid (DA), administered over a short time period, to promote the appearance of hyperplastic foci or hyperplastic nodules in diethylnitrosamine (DEN)-initiated male Fischer rats was examined. The 80 rats were divided into five groups, 15 rats in Groups 1-4 and 20 rats in Group 5. Groups 1, 3, and 5 were injected ip with DEN and later Groups 1 and 3 were fed 0.5% DA or 0.05% phenobarbital (PB), respectively, for 10 wk. Groups 2 and 4 were given saline in place of DEN and later fed DA or PB alone for 10 wk. Both DA and PB (Groups 1 and 3) promoted the development of considerable numbers of foci positive for gamma-glutamyl transferase if preceded by DEN initiation. DEN alone (Group 5) induced much fewer and relatively small foci but induced no hyperplastic nodules. Significantly more and larger foci and a considerably greater number of hyperplastic nodules were seen with DA (Group 1) than with PB (Group 3). DA without DEN (Group 2) induced a small number of foci and hyperplastic nodules. These data suggested that DA is a moderately strong promoter of preneoplastic liver lesions in the male rat. (9 Refs)

12. LIVER TUMORS INDUCED IN WISTAR RATS FOLLOWING COMBINED ADMINISTRATION OF DDT AND PHENOBARBITAL (MEETING ABSTRACT).

Barbieri O, Sanguineti M, Rossi L
Istituto Scientifico per lo Studio e la Cura dei Tumori, Genoa, Italy
Tumori; 67(2,SupplA):60 1981

Prolonged administration of dichlorodiphenyltrichloroethane (DDT) and phenobarbital (PB) induces liver tumors (hepatomas) in rats in advanced age in terms of their life span (80 wk and beyond). In the present experiment we wished to determine whether combined long-term treatment with DDT and PB reduces latency and/or favors progression of these tumors as opposed to more malignant types. Eighty male and female Wistar rats were exposed to DDT (500 ppm in the diet) and PB (500 ppm in their drinking water) till 150 wk of age. An equal number of rats was used as a control. The most significant results of this experiment are as follows: 1) liver tumors were induced only in animals in advanced age (latency unaltered); 2) combined treatment caused induction of several hepatocarcinomas while among the hepatomas observed many contained cystic conglomerates (degenerative formations not seen during separate treatment); 3) an additive effect of the 2 compounds was observed in females (83 per cent liver tumors as opposed to 55 per cent in females exposed to DDT and 32 per cent among those exposed to PB), while the incidence of such tumors remained unaltered in the males (59 per cent compared to 59 per cent with PB and 35 per cent with DDT). The observations reported clearly indicate that DDT and PB have the effect of potentiating carcinogenesis in experimental animals when administered simultaneously. That is of great importance since in human surroundings there is a prevalence of weak chemical carcinogens. Our results suggest that interaction between these compounds and human tissues may increase the oncogenic risk in our species. (no Refs) (In ITA)

13. TUMOR INDUCTION IN SYRIAN HAMSTERS FED A COMBINATION OF AMINOPYRINE AND NITRITE.

Bergman F, Wahlin T
Dept. Pathology, Univ. Umea, S-901 87 Umea, Sweden
Acta Pathol Microbiol Scand [A]; 89(3):241-245 1981

Hamsters fed an aminopyrine/sodium nitrite mixture in drinking water showed a high incidence of intrahepatic bile duct tumors. Chenodeoxycholic acid was not found to have any promoting effect on the liver carcinogenicity induced by this combination of aminopyrine and sodium nitrite in hamsters. (Author abstract) (9 Refs)

14. MODIFICATION OF LUNG TUMOR DEVELOPMENT IN A/J MICE.

Witschi HP, Hakkinen PJ, Kehrer JP
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Toxicology; 21(1):37-45 1981

Male and female A/J mice (age 6-8 wk) were divided into five groups with controls. The first group received 500 mg/kg urethan ip. One wk later weekly injections of 300 mg/kg butylated hydroxytoluene (BHT), 500, 300, or 150 mg/kg butylated hydroxyanisole (BHA), or 1,000 mg/kg vitamin E began. The second group received either 10 mg/kg 3-methylcholanthrene (3-MC), 2 injections 1 wk apart, or 7 mg/kg dimethylnitrosamine (DMN), given once. After 1 wk 4 weekly injections of 300 mg/kg BHT were begun. The third group received 500 mg/kg urethan ip, followed after 1 wk by 80 mg/kg methylcyclopentadienyl manganese tricarbonyl (MMT). The

fourth group received 400 mg/kg BHT, followed immediately by either a single injection of urethan or a continuous exposure to urethan. The last group received 400 mg/kg BHT followed after 2 wk by either 1,000 or 500 mg/kg urethan. The results show that BHT enhances the development of tumors induced by urethan, 3-MC, or DMN. BHA and vitamin E did not have this effect. MMT produced cell proliferation, but did not enhance carcinogenesis. Apparently the antioxidant property of BHT was not related to effect on tumor development. Rapidly dividing lung cells were not more susceptible to tumor development than resting lung cells. (21 Refs)

IN VITRO STUDIES OF TUMOR PROMOTERS

15. PHORBOL ESTER DRAMATICALLY INCREASES INCIDENCE OF METHOTREXATE-RESISTANT MOUSE CELLS: POSSIBLE MECHANISMS AND RELEVANCE TO TUMOR PROMOTION.

Varshavsky A
Dept. Biology, Massachusetts Inst. Technology, Cambridge, MA, 02139
Cell; 25(2):561-572 1981

I have tested the hypothesis that at least some of the unknown tumor promoters may act by facilitating gene amplification. A series of single-step selections for resistance to methotrexate, a specific inhibitor of dihydrofolate reductase (DHFR), was carried out with 3T6 cells in the presence and in the absence of a potent tumor promoter, 12-O-tetradecanoyl-phorbol-13-acetate (TPA). Incidence of methotrexate-resistant, colony-forming 3T6 cells is increased up to 100 fold if selection is carried out in the presence of TPA. For a major portion of this new TPA effect to be observed, it is sufficient to add TPA simultaneously with methotrexate. The effect of TPA on the incidence of methotrexate resistance is d etectable at less than 20 nM TPA and is max at about 200 nM TPA. Phorbol (a non-promoting analog of TPA), thymidine and dimethylsulfoxide each fail to produce any TPA-like effect in this system. DHFR gene copy numbers per cell in clones resistant to 100, 200 and 300 nM methotrexate are approx 3, 10 and 16x higher, respectively, than the DHFR gene copy number in the parental 3T6 cells. These numbers do not depend on the presence or absence of TPA during methotrexate selection. (Author abstract) (37 Refs)

16. EARLY CHANGES IN PHOSPHATIDYLCHOLINE METABOLISM IN HUMAN ACUTE PROMYELOCYTIC LEUKEMIA CELLS STIMULATED TO DIFFERENTIATE BY PHORBOL ESTER.

Cassileth PA, Suholet D, Cooper RA
Hosp. Univ. Pennsylvania, Philadelphia, PA, 19104
Blood; 58(2):237-243 1981

The HL-60 leukemia cell line derived from a human acute promyelocytic leukemia is stimulated to differentiate into macrophages within 24-48 hr after exposure to the phorbol ester, 12-O-tetradecanoylphorbol-13-acetate (TPA). We studied early alterations (within 90 min of exposure to TPA) in phosphatidylcholine metabolism in HL-60 cells and found that phosphatidylcholine synthesis by methylation of phosphatidylethanolamine was inhibited in a dose-dependent fashion. In contrast, synthesis of phosphatidylcholine from endogenous choline was enhanced and correlated inversely with the degree of inhibition of the methylation pathway. Phorbol ester congeners of TPA caused similar alterations in phosphatidylcholine metabolism in direct relationship to their capacity to induce differentiation in HL-60 cells. Perturbation of phosphatidylcholine metabolism is an early membrane event in TPA-induced HL-60 cell differentiation. (Author abstract) (44 Refs)

17. THE MODULATING EFFECT OF RETINOIDS AND A TUMOR PROMOTER ON MALIGNANT TRANSFORMATION, SISTER CHROMATID EXCHANGES, AND NA/K ATPASE.

Borek C, Miller RC, Geard CR, Guernsey D, Osmak RS, Rutledge-Freeman M, Ong A, Mrson H
Radiological Res. Lab., Dept. Radiology, Cancer Center/Inst. Cancer Res., Coll. Physicians and Surgeons, Columbia Univ., New York, NY, 10032
Ann NY Acad Sci; 359:237-250 1981

The interactions between retinoids and tumor promoting compound 12,O-tetradecanoyl-phorbol 13-acetate (TPA) were studied in mouse he eroploid C3H/10T1/2 cells and in diploid hamster embryo cells. TPA added to the culture medium immediately after irradiation with x-rays (300 rads) enhanced markedly the yield of transformed cells, while incubation with retinoids reduced the transformation rate. Retinoids were able to eliminate in an irreversible manner the promoting effect of TPA. Both retinoids and TPA had a comparatively negligible effect on the frequency of sister chromatid exchange. In both cell lines, retinoids reduced the level of Na/K ATPase, while TPA enhanced activity of the enzyme; simultaneous ex posure to retinoids and TPA resulted in the normalization of the enzyme level. (38 Refs)

18. STIMULATION BY RETINOIC ACID OF PROSTAGLANDIN PRODUCTION AND ITS INHIBITION BY TUMOR PROMOTERS IN MOUSE MYELOID LEUKEMIA CELLS.

Takenaga K
Ina-machi, Kitaadachi-gun, Saitama-ken 362, Japan
Gan; 72(4):488-497 1981

Retinoic acid induced lysozyme activity in mouse myeloid leukemia M1 cells. It also stimulated the synthesis and release of prostaglandins such as prostaglandin F2alpha, E2, and D2 by the cells. The particulate fraction of retinoic acid-treated M1 cells converted arachidonate to prostaglandins, and this conversion was almost completely inhibited by indomethacin. Retinol, retinal and retinyl acetate, but not the pyridyl analog of retinoic acid, also induced lysozyme activity and stimulated synthesis and release of prostaglandins. Indomethacin inhibited the induction of lysozyme activity by retinoic acid. The induction of lysozyme activity and the stimulation of prostaglandin E2 production were dependent on the concentration of retinoic acid. Kinetic studies showed that stimulation of prostaglandin E2 production by retinoic acid was followed by induction of lysozyme activity. The tumor promoters 12-O-tetradecanoyl-phorbol-13-acetate (TPA) and phorbol 12,13-didecanoate inhibited the induction of lysozyme activity by retinoic acid, but 4alpha-phorbol didecanoate and phorbol did not. TPA and phorbol 12,13-didecanoate, but not 4alpha-phorbol didecanoate, also inhibited the stimulation of prostaglandin E2 production by retinoic acid. These results suggest that stimulation by retinoic acid of prostaglandin E2 production in M1 cells is a prerequisite for the induction of lysozyme activity. On the other hand, both retinoic acid and TPA inhibited the induction by dexamethasone of phagocytic activity, which is a typical func-

tional marker of differentiation of M1 cells, without causing significant growth inhibition. Suboptimal concentrations of retinoic acid and TPA had synergistic inhibitory effects on the induction of phagocytic activity of M1 cells by dexamethasone. (Author abstract) (27 Refs)

19. RETINOIDS INHIBIT PROMOTER-DEPENDENT PRENEOPLASTIC PROGRESSION IN MOUSE EPIDERMAL CELL LINES.

Colburn NH, Ozanne S, Lichti U, Ben T, Yupsa SH, Wendel E, Jardini E, Abruzzo G
Lab. Experimental Pathology, NCI, Bethesda, MD, 20205
Ann NY Acad Sci; 359:251-259 1981

The mechanism of retinoid inhibition of promoter-dependent preneoplastic progression was studied in mouse epidermal JB6 cell line. Simultaneous exposure to retinoic acid (RA; 10(-8) to 10(-5) M) was found to reduce by 51-88% the yield of 12-O-tetradecanoyl-phorbol-13-acetate (TPA)-induced colonies. RA was also found to inhibit the induction of anchorage independence by other promoters such as mezerein. Since the simultaneous exposure to RA reduced the mitogenic effect of TPA by approx 10%, the targets of retinoids in antagonizing late-stage promotion by TPA were not involved in the mitogenic response. It was suggested that retinoids prevent induction of ornithine decarboxylase activity. (19 Refs)

20. MODULATION OF TERMINAL DIFFERENTIATION AND RESPONSES TO TUMOR PROMOTERS BY RETINOIDS IN MOUSE EPIDERMAL CELL CULTURES.

Yuspa SH, Lichti U, Ben T, Hennings H
In Vitro Pathogenesis Section, Lab. Experimental Pathology, NCI, Bethesda, MD, 20205
Ann NY Acad Sci; 359:260-273 1981

To evaluate the mechanism of tumor promotion in epidermis, the effect of retinoids on the induction of ornithine decarboxylase (ODC) was studied in cultured newborn mouse epidermal cells. Retinoids could delay and alter Ca++-induced terminal differentiation but could not prevent cell death. Retinoic acid (RA) was found to inhibit markedly ODC induction by tumor promoter 12,O-tetradecanoyl-phorbol-13-acetate (TPA). ODC induction by UV was less sensitive to RA. The degree of inhibition by RA after combined exposure to TPA and UV was similar to that after exposure to TPA alone. It was suggested that the unique inhibitory effect of RA on ODC induction by TPA and on tumor promotion results from membrane changes. (40 Refs)

21. TUMOR-PROMOTING PHORBOL ESTERS STIMULATE MYELOPOIESIS AND SUPPRESS ERYTHROPOIESIS IN CULTURES OF MOUSE BONE MARROW CELLS.

Sieber F, Stuart RK, Spivak JL
Clayton Laboratories Dept. Medicine, Johns Hopkins Univ. Sch. Medicine, 924 Traylor Res. Building, Baltimore, MD, 21205
Proc Natl Acad Sci USA; 78(7,part2):4402-4406 1981

Tumor-promoting phorbol esters affect the ability of mouse hematopoietic progenitor cells to form morphologically recognizable colonies in culture. They induce myeloid progenitor cells to form colonies of the monocyte/macrophage type in the absence of exogenous granulocyte/macrophage colony-stimulating factor. Conversely, similar concentrations of tumor-promoting phorbol esters inhibit the formation of colonies (bursts) by early erythroid progenitor cells, even when the culture medium contains saturating amounts of burst-promoting activity and erythropoietin. However, late erythroid progenitor cells, are not affected by phorbol esters. Only a temporary (45 min) exposure of marrow cells to phorbol esters is necessary to produce both stimulation of myeloid colony growth and inhibition of erythroid burst formation. Experiments with a radioactively labeled phorbol ester indicate a high affinity for celluiar binding sites. The ability of various phorbol esters to stimulate myeloid colony growth and to inhibit erythroid burst formation correlates well with their ability to promote skin tumors in mice. The different responses of two developmentally closely related hematopoietic progenitor cells to the same phorbol esters indica te the usefulness of these substances in the further analysis of regulatory events affecting hematopoiesis. (Author abstract) (23 Refs)

22. INHIBITION OF EPIDERMAL GROWTH FACTOR BINDING TO MOUSE EMBRYONAL CARCINOMA CELLS BY PHORBOL ESTERS MEDIATED BY SPECIFIC PHORBOL ESTER RECEPTORS.

Salomon DS
Lab. Pathophysiology, NCI, NIH, Bethesda, MD, 20205
J Biol Chem; 256(15):7958-7966 1981

Exposure of OTT-6050 mouse embryonal carcinoma (EC) cells to 12-O-tetradecanoyl phorbol-13-acetate (TPA) at 37 C results in an 80 to 90% reduction within 10 to 15 min in the specific binding capacity for [125I]-epidermal growth factor (EGF). At 37 C max specific binding of [125I]EGF occurs at 1 hr and is followed by a reduction in the binding of [125I]EGF. This decrease is temperature dependent and is not affected by TPA treatment. Scatchard analysis of the binding data indicates that the TPA-induced reduction in [125I]EGF binding is due to a decrease in the number of available EGF receptors/cell, without any change in the affinity of the receptors for EGF. Other tumor-promoting phorbol esters also inhibit [125I]EGF binding. The inhibitory effect of tumor-promoting phorbol esters on EGF binding is mediated by the interaction of these compounds with a specific receptor which is distinct from the EGF receptor. Binding of [20-3H]phorbol 12,13-dibutyrate (PDB) has been measured on EC cells, and it is specific and saturable. Saturation of specific [3H]PDB binding occurs between 25 and 35 nM at either 37 or 4 C, which correlates with the concentration of PDB producing half-max inhibition of [125I]EGF binding (50 nM). Other tumor-promoting phorbol esters inhibit [3H]PDB binding in a dose-dependent manner which parallels their activity in inhibiting [125I]EGF binding to its receptor and their tumor promoting activity in vivo. TPA is the most potent phorbol ester in competing for [3H]PDB binding with half-max inhibition at 2.5 nM. Specific binding of [3H]PDB is not directly affected by compounds such as EGF, dexamethasone, retinoic acid, insulin, transferrin, and vasopressin, but EGF can indirectly affect it. The ability of tumor-promoting phorbol esters to inhibit EGF binding may be mediated by a specific phorbol ester receptor. Furthermore, EGF may modulate the processing of phorbol ester receptors by preventing the presumptive internalization of the phorbol ester-receptor complex. (Author abstract) (46 Refs)

ANTICARCINOGENESIS BY CHEMICAL AGENTS

23. EFFECT OF VITAMIN A (VA) ON SKIN CANCER INDUCTION BY 20-METHYLCHOLANTHRENE (20-MC) IN MICE (MEETING ABSTRACT).

Hirose R, Hori M, Yamashiro K, Yoshida H
Dept. Dermatology, Nagasaki Univ., Sch. Medicine, Sakamoto-cho, Nagasaki 852, Japan
Nippon Hifuka Gakkai Zasshi; 91(3):257 1981

One hundred twenty d-d strain mice (3 wk old) were divided into three groups as follows: group 1 (30 mice), administration of 20-methylcholanthrene (20-MC) alone; group 2 (30), combined administration of croton oil and 20-MC; and group 3 (60), combined administration of vitamin A (VA) and 20-MC. The incidence and process of carcinogenicity in each group were examined by light and electron microscopy. Carcinogenicity was markedly inhibited in group 3 compared with groups 1 and 2. Tonofilaments of tumor cells and a decrease in desmosomes were observed in group 3. (no Refs) (In JPN)

MODIFICATION BY HORMONAL FACTORS

24. RELATIONSHIP OF HORMONES TO INHIBITION OF MAMMARY TUMOR DEVELOPMENT OF UNDERFEEDING DURING THE 'CRITICAL PERIOD' AFTER CARCINOGEN ADMINISTRATION (MEETING ABSTRACT).

Sylvester PW, Aylsworth CF, Van Vugt DA, Meites J
Physiology Department, Neuroendocrine Research Laboratory, Michigan State University, East Lansing, MI, 48824
63rd Annual Meeting of the Endocrine Society, June 17-19, 1981, Cincinnati, Ohio. The Endocrine Society 385 pp., 1981.

Seven days prior to 7,12-dimethyl-benz(a)anthracene (DMBA) administration, virgin 50-day old female Sprague-Dawley rats were placed on a food-restricted diet and continued on this regimen until 30 days after DMBA injection. One day prior to and seven days after DMBA administration, animals were given daily 0.1 ml sc injections of 0.9% NaCl (controls), haloperidol (HAL, 0.5 mg/kg) to increase prolactin (PRL) secretion, growth hormone (GH, 0.5 mg/kg), estradiol benzoate (EB, 1 ug/rat), or a combination of HAL, EB and GH. Drug and hormone treatments were terminated after 8 days, but underfeeding continued for 30 days after DMBA administration after which time all animals were placed on ad libitum feeding for the remainder of the 26 wk experiment. Food restriction for 7 days prior to and 30 days after DMBA administration resulted in a significant reduction in av tumor number and size by the end of the 26 wk experiment. Treatment for 8 days with EB produced a significant increase in mammary tumor incidence despite underfeeding, whereas underfed rats given the combination of HAL, EB and GH showed development and growth of mammary tumors equal to that of full-fed controls. Both EB and HAL significantly raised blood PRL levels. GH alone had no apparent effect on mammary tumor incidence. These results indicate that reduced food intake during the 'critical period' for induction of mammary tumor development throughout the 6 mo period of this experiment, and that administration of EB or the combination of EB, HAL and GH for only 8 days can counteract the inhibition by underfeeding. (no Refs)

25. EVIDENCE THAT ESTROGENS ARE PROMOTERS OF HUMAN BREAST CANCER (MEETING ABSTRACT).

Sherman B, Wallace R, Bean J
Departments of Internal Medicine and Preventive Medicine, University of Iowa, Iowa City, IA, 52242
63rd Annual Meeting of the Endocrine Society, June 17-19, 1981, Cincinnati, Ohio. The Endocrine Society 385 pp., 1981.

Estrogens have been implicated in the pathogenesis of breast and endometrial carcinoma. As part of a case-control study, postmenopausal breast cancer patients were asked about their history of menopausal estrogen use, current height and wt and recalled wt at age 18. In this study we examined the influence of estrogen use and adiposity [Quetlet index, wt/ht(2)(QI)] on the age at diagnosis of breast cancer. The mean age at breast cancer diagnosis was 61.4 +/-0.8 (standard error of the mean) yr for the entire group of women. Estrogen users had an earlier age at diagnosis 58.0 +/-1.2 yr than non-users 63.2 +/-0.9 yr. There was no relationship between age at breast cancer diagnosis and adiposity in the entire group. In the non-estrogen users there was a trend toward earlier age at diagnosis in the more obese women. By contrast, among estrogen users the earlier age at breast cancer diagnosis was most striking in the non-obese women. Similar results were observed using wt at age 18 and postmenopausal wt. These results suggest that postmenopausal estrogen use and adiposity affect the age of onset of breast cancer. The earlier age at onset in obese, non-estrogen users may be attributable to greater endogenous estrogen production. The effect of exogenous estrogens is most pronounced among non-obese women, a group traditionally considered to be at low risk. Although other interpretations are possible, these findings suggest that whether or not estrogens are carcinogens they can be implicated as promoters of human breast cancer. (no Refs)

26. A PERMISSIVE ROLE OF THE PITUITARY IN ESTROGEN-INDUCED AND DEPENDENT RENAL TUMORS (MEETING ABSTRACT).

Lin YC, Loring JM, Villee CA
Department of Biological Chemistry and Laboratory of Human Reproduction, and Reproductive Biology Harvard Medical School, Boston, MA, 02115
63rd Annual Meeting of the Endocrine Society, June 17-19, 1981, Cincinnati, Ohio. The Endocrine Society 385 pp., 1981.

Prolonged administration of estrogen by implanted pellets induces renal adenocarcinomas in hamsters. Many of these animals develop enlarged pituitaries with hyperplastic and neoplastic changes which occur especially in the pars intermedia. The pituitaries of the diethylstilbestrol (DES) implanted animals weigh 90-150 mg; those of control animals weigh 7-12 mg. The enlarged pituitaries have 9.7 x 10(-10) moles/mg protein of progesterone receptors compared to 0.75 x 10(-10) moles/mg protein in the controls. To determine whether some secretory product of the pituitary may play a role as a causative or permissive agent in renal tumorigenesis castrate male hamsters were hypophysectomized, implanted with DES pellets and tumors were transplanted under the kidney capsule two mo later. Eighty days later no tumors were evident in the kidneys of these animals. In the control series, castrate males were implanted with DES pellets and two mo later tumor tissue was transplanted under the kidney capsule. Between 60 and 85 days later seven of the eight controls had developed renal tumors. To determine the possible role of the pituitary in the primary induction of the kidney tumor, 35 castrate hypophysectomized hamsters were implanted with DES pellets. New pellets were implanted every three mo and the animals survived 12 to 15 mo. At autopsy not one of these animals had

a tumor. Control castrate animals with the same schedule of pellet implantations all developed tumors within 12 mo. Hypophysectomized castrate animals implanted with DES pellets were injected either with a combination of follicle stimulating hormone and luteinizing hormone, one ug each per day, or with prolactin, one ug per day. A control group was injected with saline. These animals survived 12 to 15 mo but none developed kidney tumors. (no Refs)

27. HORMONAL REGULATION OF EPIDERMAL TUMOR DEVELOPMENT.

Lupulescu A
Electron Microscopic Lab., Wayne State Univ., 323 Medical Res. Building, 550 East Canfield Road, Detroit, MI, 48201
J Invest Dermatol; 77(2):186-195 1981

The effects of hormones and hormone-like substances such as thyroxine, estradiol, hydrocortisone, calcitonin, prostaglandins (F2alpha, A2) or hormone deficiency (hypophysectomy, gonadectomy) on the development of carcinomas in mice and rats induced by 3-methylcholanthrene were investigated. Thyroxine, PGF2alpha, calcitonin, and estradiol markedly enhanced the development of squamous cell carcinomas and basal cell carcinomas; an inhibition occurred following hydrocortisone, hypophysectomy, and gonadectomy. DNA labeling using [3H]-thymidine and radioautography revealed that DNA synthesis in neoplastic cells is also markedly influenced by the same hormones. Tumor histology and ultrastructure are profoundly affected and an increase of epithelial pearls, hyperchromatic basophilic cells, tonofilaments, polyribosomes, and lysosomes is observed following thyroxine and PGF2alpha. An increase of keratinization and intramitochondrial granules occurred with estradiol and increased sclerosis followed calcitonin. A marked reduction of cell organelles occurred after hydrocortisone, hypophysectomy, and gonadectomy. Scanning electron microscopy shows salient changes in tumor cytoarchitecture and cell surfaces (blebs, ruffles). These findings demonstrate that hormones can change the development of carcinomas, DNA synthesis as well as their cellular differentiation and consequently may be important modulators of epidermal carcinogenesis. (Author abstract) (20 Refs)

MODIFICATION BY GENETIC FACTORS

28. DIFFERENCES IN SUSCEPTIBILITY TO THE CARCINOGENIC ACTION OF URETHANE IN HYBRID MICE (C57BL/6J X C3HF) F1 (B6C3) AND (C57BL/6J X BALB/C) F1 (B6C) (MEETING ABSTRACT).

Dragani TA, Sozzi G, Della Porta G
Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy
Tumori; 67(2,SupplA):59 1981

Beginning of the 10th day of life hybrid B6C3 and B6C mice were treated qod x 5 with ip urethane in dose of 1 mg/kg. The animals were kept under observation until they reached 8 wk of age. On macroscopic examination tumors were observed in more than 90 per cent of the animals treated. Thymic lymphomas appeared with greater frequency in the B6C3 hybrid with no difference between the sexes (54 per cent in the males, 62 per cent in the females). In the B6C hybrid this type of tumor developed more often in the females (17 per cent in the males, 28 per cent among females). Liver tumors were observed in both hybrids. They appeared sooner in the B6C3 than the B6C hybrid and no noteworthy differences between the sexes were observed whereas in the B6C hybrid females proved less susceptible. Macroscopic examination revealed lung tumors in just the B6C hybrid mice which were not especially susceptible to induction of this type of tumor (78 per cent in males, 68 per cent in females). Lung tumors were seen after the first yr of age when a considerable proportion of the B6C3 animals had already died as a result of thymic lymphomas or liver tumors. The preliminary data collected support the conclusion that both hybrids are especially suited to chemical carcinogeneis studies since they are susceptible to the induction of different types of tumors. The B6C3 hybrid inherits high susceptibility to liver carcinogenesis from its C3Hf father, while the B6C hybrid inherits its high susceptibility to pulmonary carcinogenesis from its BALB/c father. (no Refs) (In ITA)

MODIFICATION BY VIRUSES, IMMUNE FACTORS OR IRRADIATION

29. TRANSFORMATION OF CELLS IN CULTURE BY MULV AND TPA (MEETING ABSTRACT).

Rapp UR, Borchert P, Young H
Laboratory of Viral Carcinogenesis, National Cancer Institute, Bethesda, MD
RNA Tumor Viruses, May 20-24, 1981, Cold Spring Harbor, New York. Cold Spring Harbor Laboratory 294 pp., 1981.

An in vitro system was developed for the transformation of mouse epithelial cells by murine leukemia virus (MuLV) in conjunction with 12-O-tetradecanoyl phorbol-13-acetate (TPA). The target cells were MMCE C17 a cell line that can be reversibly transformed by TPA. MMCE C17 can be transformed at very low frequency by infection with ecotropic C3H/MuLV. When infection of MMCE cells was followed by growth in TPA substituted medium (100 ug/ml) and the cells were subsequently tested for growth in soft agar in the absence of TPA a dramatic increase in the frequency of transformation was observed (from 0-4 colonies/10(5) cells to 600-800 colonies/10(5) cells). Cells transformed by MuLV and TPA retained a high plating efficiency in soft agar and generally did not produce virus particles. This basic protocol was also applied to rat fibroblast cells and while background growth of rat cells in agar + TPA was higher than that observed with the MMCE cells (50-70 colonies/10(5) cells) a 2-5 fold increase in the number of agar colonies was observed after infection of the rat cells with ecotropic C3H/MuLV and subsequent treatment with TPA. (1 Ref)

OTHER RELATED STUDIES

30. INDUCTION OF HYPERPLASIA OF MOUSE EPIDERMIS BY CHOLERA TOXIN.

Kuroki T
Dept. Pathobiochemical Cell Res., Tokyo Univ. Inst. Medical Science, Takanawa, Tokyo 108, Japan
Proc Jpn Acad [B]; 57(3):100-104 1981

Injection of cholera toxin into the dorsal skin of mice was observed to induce two successive synchronous divisions of epidermal cells which resulted in transient hyperplasia without interfering with epidermal differentiation. Stock soln of the cholera toxin was prepared by dissolving it at 1 mg/ml in 0.05

M tris buffer (pH 8.0) containing 50 mg/ml lactose. Immediately before injection, the soln was diluted with cold phosphated buffered saline. Male DDD mice were given intracutaneous injections of 0.1 ml of the diluted soln in four sites in dorsal skin. The mice were sacrificed from 4-6 pm to avoid the complication of possible circadian variation of the epidermal cell cycle. Demecolcine and 3H-thymidine were injected ip 3 hr and 1 hr, respectively, prior to sacrifice. The tissues at the injection sites were examined microscopically and autoradiographically. Intracutaneous injection of the cholera toxin at doses greater than 1.0 nanog evoked an acute reaction at the site of injection. Histologically, mitotic stimulation and hyperplasia of the epidermis and edematous change with granulocyte filtration of the dermis were the most prominent features of the skin lesions. This method was thought to be applicable to two-stage carcinogenesis of mouse skin for the purpose of investigating the possible correlation between epidermal hyperplasia and tumor promotion. (6 Refs)

31. CARCINOGENESIS AND AGING. I. MODIFYING EFFECTS OF AGING ON N-METHYL-N-NITROSOUREA-INDUCED CARCINOGENESIS IN FEMALE RATS.

Anisimov VN
Lab. Experimental Tumors, N. N. Petrov Res. Inst. Oncology, 68, Leningradskaya Str., Pesochny-2, Leningrad, 188646, USSR
Exp Pathol (Jena); 19(2):81-90 1981

Three- or 14-mo-old female rats were injected iv with N-nitroso-N-methylurea (MNU), 50 mg/kg body wt, 2 or 4x/wk. There was a direct correlation between the incidence of mammary carcinomas and MNU doses. Kidney tumors occurred inversely proportional to the dose of the carcinogen. Mammary adenocarcinomas were only observed in young MNU-treated rats. Cervicovaginal malignant tumors were only observed in old MNU-treated rats. The incidence of hematopoietic system tumors was the same in animals of bo th age groups. Rats treated with MNU showed acceleration of benign spontaneous tumor development. The effect of aging on the initial stage of MNU-induced carcinogenesis is believed to be determined by age-associated changes in the proliferative activity of target tissues. The effect of aging on the further development of carcinogenesis may be caused by age-associated hormonal, metabolic, and immunological shifts. (Author abstract) (42 Refs)

32. COLOSTOMY CLOSURE PROMOTES CELL PROLIFERATION AND DIMETHYLHYDRAZINE-INDUCED CARCINOGENESIS IN RAT DISTAL COLON.

Terpstra OT, Dahl EP, Williamson RC, Ross JS, Malt RA (c/o Malt), Massachusetts General Hosp., Boston, MA, 02114
Gastroenterology; 81(3):475-480 1981

The influence of adaptive cell proliferation on colonic carcinogenesis was studied in male Fischer rats with a defunctioning transverse colostomy that was closed 4 wk later. Control observations were made in other rats after colonic transection, repeated at 4 wk, after laparotomy alone, or after permanent colostomy. Tumors were induced by 1,2-dimethylhydrazine (total dose, 300 mg/kg) over 11 wk, starting 2 days after the second operation. After creation of the colostomy, amounts of protein, RNA, and DNA in the distal colon halved in 4 wk (p less than 0.001), but returned to normal 7 days after restoration of colonic continuity. This reactive hyperplasia promoted the development of distal colonic carcinomas, as compared with rats having repeated transection of the bowel (incidence 32% vs 6%, p less than 0.03). Although the amounts of protein and nucleic acid in the proximal colon were unchanged by transverse colostomy, values increased by 18%-59% 4 wk after colostomy closure ($p = 0.05$-0.002); nonetheless, the yield of tumors in this segment was unaltered. Suture-line cancers were more common after repeat transection than after colostomy closure (76% vs 39%; p less than 0.01). These data confirm the promotional effect of increased cell proliferation on intestinal carcinogenesis. (Author abstract) (40 Refs)

33. CANCER LINK TO MAGNETIC FIELD EXPOSURE: A HYPOTHESIS.

Easterly CE
Health and Safety Res. Div., Oak Ridge Natl. Lab., PO Box X, Oak Ridge, TN, 37830
Am J Epidemiol; 114(2):169-174 1981

The relationship between cancer and magnetic field exposure is discussed. A cancer model for two-step (initiation and promotion) carcinogenesis is described. On the basis of existing data, exposure to magnetic fields alone would not be expected to give rise to malignant tumors. Experiments with static magnetic fields have provided only marginal evidence that magnetic field exposures could result in genetic alterations or initiations. Data indicating the magnetic fields might function as weak promotors is considered. (66 Refs)

REVIEWS

34. TUMOR PROMOTING AGENTS.

Tsilimigras CW
Natl. Inst. for Virology, Private Bag X4, Sandringham, Johannesburg 2131, South Africa
S Afr J Sci; 77(3):100-103 1981

The effects of tumor promoting agents, particularly the phorbol ester 12-O-tetradecanoyl-phorbol-13-acetate (TPA) on cells in vitro are considered. The major diterpene ester of croton oil, TPA has been shown to be the most potent promoter of multiple skin tumors in vivo. It has also been found to induce many different responses in vitro, including enhancement of transformation, stimulation of a number of specific enzymes and cyclic nucleotides, modifications in macronucleotides, modifications in macromolecular synthesis, an inhibition of terminal differentiation, changes in cellular membranes and cellular morphology, and disturbances of the transport of cations and small molecules through membranes. TPA has been reported to enhance the degree of the in vitro transformation of fibroblast cell cultures and rat embryo cells previously exposed to polycyclic aromatic hydrocarbons, UV light, or adenoviruses. TPA has also been found to enhance the expression of transformation by Rous sarcoma virus in chick embryo fibroblasts. TPA had been shown to induce ornithine decarboxylase, protease, and plasminogen activator. TPA seems to stimulate DNA and RNA synthesis. Other classes of possible tumor promoters, such as melittin, phenol, oleic acid, some non-aromatic hydrocarbons, Tween 60, saccharin, and cyclamate, are discussed. (16 Refs)

35. HYPOTHESES ON THE MOLECULAR MECHANISM OF ACTION OF TUMOR PROMOTERS.

Smythies JR
Dept. Psychiatry, Univ. Alabama, Birmingham, AL, 35294
Med Hypotheses; 7(6):711-717 1981

A number of alternative hypotheses of the molecular mechanism of action of tumor promoters related to tetradecanoyl phorbol acetate (TPA) are presented. These hypotheses are based on current experimental evidence and the molecular structure of these agents in relation to the molecular structure of phospholipase A2 (PLA2) as revealed by xray crystallography. The facts explained and correlated are as follows: TPA causes inflammation, hyperplasia, induction of ornithine decarboxylase activity, and tumor promotion. Some relatives of TPA share these effects, whereas others share all of the effects except the tumor promoting ability. Others lack all of the activities. Possible molecular bases for two-stage tumor promotion are described. It was suggested than an interaction with the lipid bilayer may be significant for Stage 1 promotion as a necessary, but not sufficient, factor for tumor promotion. It was also suggested that Stage 2 promotion may involve activation of PLA2, possibly by activation of pronase. The biological significance of the observed stereochemical complementarity between the molecule of TPA and groove 1 on PLA2 is discussed. The nature of the endogenous ligand at the postulated TPA receptor is considered. Experiments that may test the hypothesis are described. (15 Refs)

36. INFLUENCE OF NONCARCINOGENIC SECONDARY FACTORS ON RADIATION CARCINOGENESIS.

Little JB
Lab. Radiobiology, Harvard Univ., Sch. Public Health, Boston, MA, 02115
Radiat Res; 87(2):240-250 1981

The results of experiments on the role of secondary factors in the expression of radiation-induced malignant transformation and carcinogenesis are reviewed. Experiments with mouse embryo fibroblasts (C3H 10T1/2 and BALB/3T3 cell lines) showed that approx 13 or 8-9 rounds of cell division were required for transformation to be fully expressed in x-irradiated cells. Delay of subcultivation for 24-48 hr resulted in marked decrease of the transformation frequency. Irradiation of cells with 25 rads followed by exposure to nonmutagenic dose of 12-O-tetradecanoyl-phorbol-13-acetate (active ingredient of croton oil) increased the transformation frequency to the level recorded after irradiation with 200-300 rads. Such agents as saccharin and endogenous epidermal growth factor were also shown to promote malignant transformation in vitro. Incubation of irradiated cells with inhibitors of proteolytic enzymes, vitamin A, or vitamin C was shown to inhibit malignant transformation. These findings suggest that the initial radiation-induced alteration may be a reversible epigenetic event involving an alteration in gene expression. Intratracheal instillations of isotonic saline was shown to increase the frequency of lung cancer in irradiated hamsters (36% compared with 2% in animals subjected to irradiation alone). These findings indicate that the effect of noncarcinogenic secondary factors are not restricted to in vitro transformation systems. (38 Refs)

37. EXPERIMENTAL APPROACHES TOWARDS THE BIOCHEMICAL ANALYSIS OF CHEMICAL CARCINOGENESIS.

Laishes BA
McArdle Lab. for Cancer Res., Univ. Wisconsin Medical Sch., Madison, WI, 53706
ACS Symp Ser; 160:197-215 1981

Developments in chemical carcinogenesis research as they affect the understanding of malignancy at the molecular level are reviewed. Early observations noted the relationship between exposure of humans to certain substances and the occurrence of certain cancers. This led to laboratory experiments demonstrating the induction of cancers in animals by purified chemicals. Carcinogenesis was further depicted as a two-stage process. The first step involved initiation of cancer potential in cells by a carcinogen. The second step involved promotion of cancer development by a promoting substance that might be different from the initiator. The importance of the presence of various antagonistic carcinogens, enzymes, and metabolites of carcinogens was recognized as affecting the development of cancer or the lack of it. Molecul ar analysis showed that carcinogens are electrophilic molecules that bind to the DNA molecules in target cells. Current research is exploring the importance of cell cycle phase on carcinogenesis. Cell lineage and genotypic cell markers are being studied as tools for cancer research. (91 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. THE GENETIC TOXICOLOGY OF ALDRIN AND DIELDRIN.
Ashwood-Smith MJ
Environmental Toxicology Res. Group, Dept. Biology, Univ. Victoria, Victoria, BC V8W 2Y2, Canada
Mutat Res; 86(2):137-154 1981

RADIATION CARCINOGENESIS

2. EFFECTS OF LOW-LEVEL RADIATION ON BIOLOGIC SYSTEMS: A LITERATURE REVIEW.
Best TL, Hoditschek B
Eastern New Mexico Univ., Portales, NM
Effects of Low-Level Radiation on Biologic Systems: A Literature Review. Available from National Technical Information Service, Springfield, VA, as SAND-80-7143., 246 pp., 1981.

3. PHOTOCARCINOGENESIS: AN OVERVIEW.
Forbes PD
Skin and Cancer Hosp., 3322 North Broad St., Philadelphia, PA, 19140
J Invest Dermatol; 77(1):139-143 1981

DIETARY FACTORS IN CARCINOGENESIS

4. EPIDEMIOLOGICAL CORRELATIONS BETWEEN DIET AND CANCER FREQUENCY.
Correa P
Louisiana State Univ. Medical Center, New Orleans, LA, 70112
Cancer Res; 41(9,part2):3685-3689 1981

5. ROLE OF DIETARY FIBER IN DIVERTICULAR DISEASE AND COLON CANCER.
Talbot JM
Life Sciences Res. Office, Federation of American Societies for Experimental Biology, Bethesda, MD, 20014
Fed Proc; 40(9):2337-2342 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

6. PRIMARY HEPATIC CANCER IN ALCOHOLICS.
Tamburro CH, Lee HM
Liver Res. Center, Div. Digestive Diseases and Nutrition, Univ. Louisville Health Sciences Center, 511 South Floyd St., Louisville, KY, 40232
Clin Gastroenterol; 10(2):457-477 1981

7. PANCREATIC CANCER AND ALCOHOL.
Okuda K, Ohnishi K
Dept. Medicine, Chiba Univ. Sch. Medicine, 1-8-1 Inohana, Chiba City (280), Japan
Clin Gastroenterol; 10(2):479-484 1981

8. HELMINTHS IN THE INDUCTION OF CANCER. II. SCHISTOSOMA HAEMATOBIUM AND BLADDER CANCER.
Schwartz DA
Inst. Medicine, Far Eastern Univ., Manila, Philippines
Trop Geogr Med; 33(1):1-7 1981

9. GENETICS OF WILMS'S TUMOR.
Matsunaga E
Dept. Human Genetics, Natl. Inst. Genetics, Mishima, Shizuoka-Ken, 411, Japan
Hum Genet; 57(3):231-246 1981

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

10. NEOPLASMS: COMPARATIVE PATHOLOGY OF GROWTH IN ANIMALS, PLANTS, AND MAN.
Kaiser HE
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MODIFICATION OF CARCINOGENESIS

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TUMOR PROMOTION AND COCARCINOGENESIS IN MOUSE SKIN

1. EFFECTS OF 3-ISOBUTYL-1-METHYLXANTHINE AND CYCLIC NUCLEOTIDES ON 12-O-TETRADECANOYLPHORBOL-13-ACETATE-INDUCED ORNITHINE DECARBOXYLASE ACTIVITY IN MOUSE EPIDERMIS IN VIVO.

Perchellet JP, Boutwell RK
McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI, 53706
Cancer Res; 41(10):3918-3926 1981

A single topical application of 8.5 nmol of 12-O-tetradecanoylphorbol-13-acetate (TPA) to mouse skin induced rapid and transient increases in the levels of both guanosine cyclic 3':5'-monophosphate and adenosine cyclic 3':5'-monophosphate, followed by the stimulation of ornithine decarboxylase (ODC , L-ornithine carboxy-lyase, EC 4.1.1.17) activity. Peak synthesis of guanosine cyclic 3':5'-monophosphate and adenosine cyclic 3':5'-monophosphate were achieved within 10 and 60 min, respectively, while ODC activity was max stimulated between 4.5 and 6 hr. The increased levels were dose dependent and correlated with the tumor-promoting abilities of diverse compounds. However, the magnitudes of the cyclic nucleotide and ODC responses to TPA were quite different (3-to 7-and 70-fold, respectively). A single topical application of 10 umol of 3-isobutyl-1-methylxanthine (IBMX), which was able to raise the levels of cyclic nucleotides almost as much as did TPA, produced only a 9-fold increase in ODC activity. IBMX, as well as other phosphodiesterase inhibitors, enhanced the magnitude and the duration of the increases in cyclic nucleotide levels and ODC activity produced by TPA. Max stimulation of TPA-induced ODC activity was achieved when IBMX was applied within the 30-min interval preceding TPA treatment. As a result of the IBMX pretreatment, the same or higher levels of cyclic nucleotides and ODC activity could be induced with about 10x less TPA or with weak and moderate tumor promoters, as compared with the increased levels attributable to TPA alone. However, in the presence of IBMX, a discrepancy was still observed between the magnitude of the increased cyclic nucleotide response to TPA (6-to 14-fold) and the 150-fold induction of ODC activity produced by TPA. In addition, single or combined topical treatments with guanosine cyclic 3':5'-monophosphate and adenosine cyclic 3':5'-monophosphate were unable to mimic the effect of TPA on ODC activity and even depressed significantly basal and TPA-induced ODC activities in the presence of IBMX. Therefore, the findings presented in this and an accompanying paper suggest that, in mouse epidermis in vivo, if TPA-increased cyclic nucleotides participate in the molecular mechanism by which ODC activity is induced, their controlled degradation may be equally important. (Author abstract) (60 Refs)

2. EFFECTS OF 3-ISOBUTYL-1-METHYLXANTHINE AND CYCLIC NUCLEOTIDES ON THE BIOCHEMICAL PROCESSES LINKED TO SKIN TUMOR PROMOTION BY 12-O-TETRADECANOYLPHORBOL-13-ACETATE.

Perchellet JP, Boutwell RK
McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI, 53706
Cancer Res; 41(10):3927-3935 1981

The phosphodiesterase inhibitor 3-isobutyl-1-methylxanthine (IBMX), which enhances 12-O-tetradecanoylphorbol-13-acetate (TPA)-stimulated cyclic nucleotide levels and ornithine decarboxylase (L-ornithine carboxy-lyase, EC 4.1.1.17) activity in mouse epidermis in vivo, was tested for its ability to modify the process of skin carcinogenesis using the initiation-promotion (two-step) model system for the production of skin tumor in mice. Topical application of 10 umol of IBMX prior t o each promotion with 8.5 nmol of TPA reduced by 78% the number of papillomas per mouse. The inhibition was dose dependent. All phosphodiesterase inhibitors tested inhibited the development of skin papillomas. Topical applications of guanosine cyclic 3':5'-monophosphate and/or adenosine cyclic 3':5'-monophosphate before each treatment with TPA were also very effective in inhibiting the formation of skin papillomas. Combined treatments including IMBX, guanosine cyclic 3':5'-monophosphate and adenosine cyclic 3':5'-monophosphate reduced by 98% the incidence of skin papillomas promoted by TPA. However, IBMX treatment 24 hr after each promotion with TPA did not suppress the formation of skin papillomas. Futhermore, repeated applications of IBMX before or after initiation with 7,12-dimethylbenz[a]anthracene did not alter the development of skin tumors. These results indicate that phosphodiesterase inhibitors and cyclic nucleotides inhibit the promotion of skin papillomas. Indeed, these modifiers act on some of the biochemical events proposed to be necessary components of the carcinogenesis process. They inhibit dramatically both TPA-increased polyamine levels and TPA-stimulated RNA, protein, and DNA synthesis. Combined treatments including IBMX and cyclic nucleotides produced additive inhibitions of polyamine, RNA, protein, and DNA synthesis in relation with their greater reduction of the formation of skin papillomas. Since IBMX and cyclic AMP block the usual accumulation of putrescine and spermidine produced by TPA in mouse epidermis in vivo and inhibit the activity of ornithine decarboxylase when added in the assay mixture, these compounds may actually interact directly with the enzyme in situ as other ornithine decarboxylase inhibitors do. (Author abstract) (50 Refs)

3. TUMOR PROMOTION BY FOREIGN BODIES (IUD).

Ryan WL, Stenback F, Curtis GL
Dept. Biochemistry, Univ. Nebraska Medical Center, South Lab., Room 3018, 42nd and Dewey Ave., Omaha, NE, 68105
Cancer Lett; 13(4):299-302 1981

The effect of implanted commercial intrauterine device (IUD) fragments on production of tumors initiated with 7,12-dimethylbenzanthracene (DMBA) was studied in strain A female mice. Two wk after sc or ip insertion of 4-7 mm Lippes Loop or Cu-7 IUD fragments, topical DMBA application (25 ug qod) in the shaved interscapular area was begun, for a total of 200 ug DMBA/mouse. Treatment groups received (1) DMBA only, (2) DMBA + Lippes Loop sc, (3) DMBA + Lippes Loop ip, or (4) DMBA + Cu-7 ip. Respective rates of mice having tumors were 20% (2 papillomas, 2 keratoacanthomas, mean size 19 square mm (mm2)), 33% (4 papillomas, 1 squamous cell carcinoma, 1 gross identification only, size 20 mm2), 60% (9 papillomas, 1 keratoacanthoma, 3 squamous cell carcinomas, 4 gross identification, size 38 mm2), and 66% (19 papillomas, 5 squamous cell ca rcinomas, 1 gross identification, size 40 mm2). Tumor development in groups 3 and 4 was significantly different from that in group 1; tumor appearance was faster (8 and 10 wk, respectively, vs 16 wk) and tumor size was twice as large. IUDs employed as foreign bodies apparently promote skin carcinogenesis by the carcinogen DMBA. The result is particularly striking when the IUD is implanted ip; evidently, promotion and initiation need not occur in the same place. Autoantibodies may be one of the means of tumor promotion. (9 Refs)

4. EFFECT OF NOCARDIA RUBRA CELL-WALL SKELETON TREATMENT ON TUMOR FORMATION IN TWO-STAGE CHEMICAL CARCINOGENESIS OF MOUSE SKIN.

Inoue T, Yoshimoto T, Ogura T, Hirao F, Azuma I, Yamamura Y
The Third Dept. Internal Medicine, Osaka Univ. Medical Sch., Fukushima 1-1-50, Fukushima-ku, Osaka 553, Japan
Cancer Immunol Immunother; 11(3):207-210 1981

Male C57BL/6 mice were painted at age 11 wk on the dorsal skin with 20 ug 7,12-dimethylbenz[a]anthracene (DMBA). Beginning 7 wk later they were painted with 2.5 ug 12-O-tetradecanoyl-phorbol-13-acetate (TPA) 2x/wk for 30 wk. Three groups of mice were treated with sc injections of 100 ug Nocardia rubra cell-wall skeleton (N-CWS) 1x/wk for 7 wk. Group 1 received the N-CWS before initiation with DMBA. Group 2 received N-CWS between initiation and promotion with TPA. Group 3 received N-CWS beginning at the start of promotion. A fourth group recieved no N-CWS treatment. All N-CWS-treated groups showed prolongation of the latent period before appearance of the first tumor. Group 1 exhibited the most significant reduction in incidence of skin tumor (5/17 30 wk from the beginning of promotion vs 13/19 in Group 4) and number of tumors/survivor (0.35 at 30 wk vs 1.74 in Group 4). N-CWS was effective in group 3 until 20 wk after the beginning of promotion. It was also effective in group 2 at 15 wk after the beginning of promotion, but overall tumor yield was the same in groups 2 and 4. N-CWS may inhibit carcinogenesis by enhancing immunological surveillance at the promotion stage or by activating macrophages which sequester DMBA. (24 Refs)

TUMOR PROMOTION AND COCARCINOGENESIS IN OTHER ANIMAL MODELS

5. FAILURE TO DISCRIMINATE INITIATION FROM PROMOTION OF LIVER TUMORS IN A LONG-TERM STUDY WITH THE PHENOBARBITAL-TYPE INDUCER ALPHA-HEXACHLOROCYCLOHEXANE AND THE ROLE OF SUSTAINED STIMULATION OF HEPATIC GROWTH AND MONOOXYGENASES.

Schulte-Hermann R, Parzefall W
Institut fur Toxikologie und Pharmakologie, Pilgrimstein 2, 335 Marburg, W. Germany
Cancer Res; 41(10):4140-4146 1981

The compound alpha-hexachlorocyclohexane (alpha-HCH) was administered po to female Wistar rats for periods of up to 33 mo; doses were 20 mg/kg/day, 200 mg/kg every 2nd wk, or 420 mg/kg every 3rd wk. Increases of liver size, DNA, RNA, and protein (by 50 to 100%) and of drug-metabolizing enzyme acti vities (up to 300%) observed previously after single doses of alpha-HCH were found to persist after approx 1/3, 1, and 2 yr of treatment. At 1 and 2 yr, DNA synthesis was measured by [3H]thymidine uptake and was no higher than in controls. All changes regressed upon withdrawal of alpha-HCH after 1 yr of treatment. These findings provide no evidence to suggest a protracted development of toxicity or of growth autonomy in the majority of liver cells. Foci of altered cells, neoplastic nodules, and in 2 animals hepatocellular carcinoma were detected histologically in the livers of 24 of 34 treated rats. In livers of 10 of 22 untreated control rats, foci of altered cells developed 'spontaneously' between 12 and 34.5 mo. If neoplastic lesions were induced by a single dose of diethylnitrosamine, 75 or 150 mg/kg, subsequent treatment with alpha-HCH led to the appearance of hepatocellular carcinoma within 7 mo. Altogether, hepatocellular carcinomas were found in 18 of 21 rats treated with both agents but in only 3 of 26 animals treated with diethylnitrosamine alone. The results show that determination of tumor numbers alone in a long-term animal experiment does not allow one to decide whether alpha-HCH (and similar 'xenobiotic inducers') is an initiating carcinogen or merely promotes tumorigenesis from 'spontaneous' lesions. Our findings support the latter possibility by the failure to detect evidence suggesting initiating potential of alpha-HCH, by the enhanced mitotic response to alpha-HCH in foci of altered cells as reported elsewhere, and by the observation of a permanent stimulatory action on liver growth during prolonged exposure to alpha-HCH. (Author abstract) (46 Refs)

6. ENZYME DEVIATION PATTERNS IN PRIMARY RAT HEPATOMAS INDUCED BY SEQUENTIAL ADMINISTRATION OF TWO CHEMICALLY DIFFERENT CARCINOGENS.

Sato K, Hatayama I, Hoshino K, Imai F, Tsuchida S, Sato T, Nishimura K, Tatematsu M, Ito N
Second Dept. Biochemistry, Hirosaki Univ. Sch. Medicine, Hirosaki 036, Japan
Cancer Res; 41(10):4147-4153 1981

Enzyme deviation patterns were examined in primary rat hepatomas induced by short-term sequential administration of two chemical carcinogens from among 2-fluorenylacetamide (FAA), diethylnitrosamine (DENA), and 3'-methyl-4-dimethylaminoazobenzene (3'-Me-DAB) or by FAA or 3'-Me-DAB followed by phenobarbital as a promoter. The purpose was to discern how the patterns are influenced by different administration schedules of carcinogens and which of the two carcinogens in the sequence affects the patterns more. Biochemical differentiation of hyperplastic hepatic nodules and hepatomas was determined by simultaneous assays of activities and isozyme composition of glucose-adenosine triphosphate phosphotransferase, pyruvate kinase, glucose-6-phosphatase, fructose-1,6-biphosphatase, and gamma-glutamyltransferase with consideratio of histological classification of nodules and tumors. Poorly differentiated hepatomas were predominantly induced by 3'-Me-DAB followed by FAA or DENA except for hepatomas induced by 3'-Me-DAB followed by phenobarbital, which were mainly well and moderately differentiated; well and moderately differentiated hepatomas were predominantly induced by FAA followed by 3'-Me-DAB or phenobarbital. The degree of enzyme deviation of the hepatomas induced by DENA as the first carcinogen was intermediate between those of hepatomas induced by FAA or 3'-Me-DAB, although the degree tended to increase with increased dose or term of DENA. These results indicate that deviations of some enzymes, such as pyruvate kinase and fructose-1,6-bisphosphatase, as well as histological differentiation of the primary hepatomas are more strongly influenced by the first carcinogen than by the second under our administration schedules and that the degree of enzyme deviation shown by hepatomas produced by a particular carcinogen treatment regimen principally relates to the potential of that regimen to induce the more anaplastic tumors. (Author abstract) (33 Refs)

7. INFLUENCE OF ETHYL ALCOHOL ON CARCINOGENESIS WITH N-NITROSODIMETHYLAMINE.

Griciute L, Castegnaro M, Berezist JC
Inst. Epidemiology, Microbiology, and Hygiene, 64 Gorki St., Vilnius 232024, Lithuania, USSR
Cancer Lett; 13(4):345-352 1981

The carcinogenic action of N-nitrosodimethylamine (NDMA; 0.03 mg by gavage x 2/wk) administered for 50 wk in either water or 40% ethanol was examined in 208 C57BL 8-wk-old mice. The mice were divided into the following treatment groups: (1) NDMA in ethanol, (2) NDMA in water, and (3) ethanol only. Death from tumors in groups 1 and 2 began, respectively, at wk 30 and 38; all group 3 subjects survived beyond 50 wk. Most notably, frontal brain lobe malignant tumors appeared only in group 1. Greyish infiltrating masses arising from the posterior nasal fossa were detected in 12/36 males and 12/30 females. Tumors were microscopically identical; histological appearance was typical of olfactory neuroepithelioma. No metastases were found. Groups 1 and 2 exhibited other malignant and benign liver tumors and lymphomas. Lymphomas and benign tumors were also found in group 3. Tumor rate (21%) was significantly lower in group 3 than in groups 1 (48%) and 2 (43%); morbidity for malignant liver tumors was significantly lower in group 1 (16%) than in group 2 (30%). Alcohol by itself was not carcinogenic but was associate a change in target for the liver carcinogen NDMA: development of infiltrating olfactory neuroepithelioma was favored. (14 Refs)

8. EFFECTS OF CHLOROFORM AND DIMETHYLNITROSAMINE ON RENAL CARCINOGENESIS IN UNILATERALLY NEPHRECTOMIZED RATS FED FORMIC ACID 2-[4-(5-NITRO-2-FURYL)-2-THIAZOLYL]HYDRAZIDE.

Hirose M, Imaida K, Ito H, Hayashi M, Ishihara Y, Ito N
First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan
Carcinogenesis; 2(8):703-708 1981

Male Fischer rats were divided into five groups. Group 1 was subjected to unilateral nephrectomy (UN). After 2 days dimethylnitrosamine (DMN: 20 mg/kg body wt) was injected ip. One wk after UN the rats were placed on a diet containing 0.2% 2-[4-(5-nitro-2-furyl)thiazolyl]hydrazide (FNT). Two wk after UN they received CHCl3 (400 mg/kg body wt). Group 2 received the same treatment without the FNT diet. Group 3 received the same treatment as group 1, except that CHCl3 treatment came before UN. Group 4 received the same treatment as group 3, but without FNT. Group 5 received only the FNT diet. Rats from each group were studied at 8, 16, and 32 wk. Renal tubular hypertrophy was found in 100% of groups 1, 3, and 5 at all three times. Tubular hyperplasia was found in group 1 (0%, 53.3%, 100%), group 3 (20%, 52.9%, 94.4%) and group 5 (0%, 0%, 94.1%) at 8, 16, and 32 wk, respectively. Renal cell tumors were found at 32 wk in groups 1 (85%), 3 (88.9%), and 5 (17.6%). No tumors were found in groups 2 and 4. The results From groups 2 and 4 show little or no initiating effect for FNT. Slight enhancement of renal tumors was produced by UN. The results from groups 1 and 3 indicate that UN and CHCl3 treatments had about equal effect in inducing preneoplastic changes in rat kidney. The enhancement of tubular hyperplasia and renal cell tumors by combined treatment with CHCl3, DMN, UN, and FNT in the initiating and promoting stages was confirmed. (22 Refs)

IN VITRO STUDIES OF TUMOR PROMOTERS

9. MOUSE SKIN CELLS RESISTANT TO TERMINAL DIFFERENTIATION ASSOCIATED WITH INITIATION OF CARCINOGENESIS.

Yuspa SH, Morgan DI
Lab. Experimental Pathology, NCI, Bethesda, MD, 20205
Nature; 293(5827):72-74 1981

The dorsal epidermis of 7-8-wk-old BALB/c and SENCAR mice in the resting phase of the hair cycle was painted once with a tumor-initiating dose of 7,12-dimethylbenz[a]anthracene (DMBA; 25 ug/200 ul acetone) followed by 5 ug of the promoter 12-O-tetradecanoyl phorbol-13-acetate (TPA) in 200 ul acetone, 2 x/wk for 4 wk beginning 7 days after DMBA application. Controls received acetone only. Either 3 days or 1 wk after the last application of TPA or acetone, the mice were sacrificed and their dorsal skin cultured under conditions that permit selection of differentiation-resistant foci. Only 2/99 dishes derived from epidermis of noninitiated BALB/c mice with or without TPA contained foci resistant to Ca++-induced terminal differentiation, and the colonies were very small and relatively pale, whereas 50-60% of the dishes derived from initiated BALB/c mice contained differentiation-resistant colonies that were mostly either confluent o r dark red, and large. The SENCAR line, bred for sensitivity to skin carcinogenesis, behaved differently: dishes derived from epidermis of noninitiated mice with and without TPA and dishes derived from epidermis of initiated and promoted mice showed equal numbers of positive results (7/29 plates), while dishes from initiated, unpromoted mice yielded approx 60% (18/30) positive plates. Thus, SENCAR epidermis appears to contain preexisting initiated cells; the reduction of positive plates in the initiated and promoted group may have been due to cytotoxicity associated with TPA application in this mouse strain. The differentiation-resistant assay reported here appears to be of use in recognizing and quantitating the alteration in regulation of normal differentiation that is postulated to be an early event in chemical carcinogenesis. (17 Refs)

10. EFFECTS OF 12-O-TETRADECANOYL PHORBOL-13-ACETATE AND EPIDERMAL GROWTH FACTOR ON THE PROLIFERATION OF HUMAN MUTANT FIBROBLASTS IN VITRO.

Gansler T, Kopelovich L
(c/o Kopelovich), Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Cancer Lett; 13(4):315-323 1981

The role of cell density in the response of cultured skin fibroblasts (SF) from individuals with hereditary adenomatosis of the colon and rectum (ACR) and from normal individuals to 12-O-tetradecanoyl phorbol-13-acetate (TPA) and to epidermal growth factor (EGF) was examined. The effect of TPA and EGF on the morphology of cell clones was also studied. Treatment of high density (6 x 10(4) cells/square cm) ACR-SF cultures with TPA produced dose-dependent stimulation of cell proliferation over the entire (0.5-100 nanog/ml) range tested. Addition of TPA to sparse (4.75 x 10(3) cells/square cm) cultures resulted in biphasic dose-response, with max inhibition at 2.0-10 nanog/ml. Similar results were found with normal human SF, primarily in sparse cultures, but these cells were more sensitive than ACR-SF. Normal SF in dense culture were not responsive to TPA stimulation. EGF (0.01-10 nanog/ml) was mitogenic in both sparse and confluent ACR-SF cultures in a dose-dependent manner. At EGF levels above 50

nanog/ml, however, inhibition of cell proliferation became apparent. Normal SF responded similarly. TPA exposure induced formation of dendritic-like cells with irregular thin cytoplasmic processes in both cell types. ACR-SF exposed to EGF were more densely packed and spindle-shaped, with more parallel orientation in the periphery. The results suggested that EGF and TPA share one of two existing TPA receptors; the higher affinity (unshared) receptor becomes saturated at ligand concentrations below 10 nanog/ml. TPA inhibition in sparse culture reflects the extent of neoplastic transformation; the less sensitive tumor cells apparently lack the higher affinity receptors. (26 Refs)

11. INITIATION OF C3H 10T1/2 CELL TRANSFORMATION BY FORMALDEHYDE.

Ragan DL, Boreiko CJ

(c/o Boreiko), Chemical Industry Inst. Toxicology, P. O. Box 12137, Research Triangle Park, NC, 27709

Cancer Lett; 13(4):325-331 1981

The ability of formaldehyde to transform C3H/10T-1/2 Cl 8 cells and to act as an initiating agent for the process of transformation in the presence of 0.1 ug/ml 12-O-tetradecanoyl phorbol-13-acetate (TPA) was examined. Treatment with 0.1-2.5 ug/ml formaldehyde alone did not result in significant rates of transformation. Following 0.1-1.0 ug/ml formaldehyde with TPA treatment produced transformed foci in an increasing dose-dependent manner. Focus production declined at 2.5 ug/ml formaldehyde. A max 1.6 x 10(-3) foci/surviving cell were observed at 1.0 ug/ml; type II foci outnumbered type III 4:1. Neither methanol nor formic acid demonstrated significant transforming or initiating ability. The results suggest that formaldehyde is an initiating agent for C3H/10T-1/2 Cl 8 transformation. Study of such compounds should include chemical treatment which precedes exposure to tumor promoters. (14 Refs)

12. TUMOUR PROMOTOR PHORBOL-12-MYRISTATE-13-ACETATE INDUCES CHROMOSOMAL DAMAGE VIA INDIRECT ACTION.

Emerit I, Cerutti PA

Lab. Experimental Cytogenetics, Institut Biomedical des Cordeliers, Universite Pierre et Marie Curie, 15, Rue de l'Ecole de Medecine, Paris VI, France

Nature; 293(5828):144-146 1981

The clastogenicity of the strong skin tumor promoter phorbol-12-myristate-13-acetate (PMA), the weak promoter 4-O-methyl-phorbol-12-myristate-13-acetate and the nonpromoter phorbol (P) was compared in phytohemagglutinin-stimulated human lymphocytes. PMA (10 nanog/ml) induced many chromosome aberrations; 4-O-methyl-PMA induced a significant increase in aberrations only at the highest dose (1,000 nanog/ml); and P was completely inactive. The aberration frequencies increased with an increase in PMA exposure from 4 to 72 hr. PMA also induced polyploidization in 72-hr cultures, but it was a weak inducer of sister chromatid exchanges. Superoxide dismutase inhibited the induction of chromosome aberrations, indicating that superoxide radicals were intermediates in aberration formation. (28 Refs)

13. REGULATION OF PLASMINOGEN ACTIVATOR IN 3T3 CELLS: EFFECT OF PHORBOL MYRISTATE ACETATE ON SUBCELLULAR DISTRIBUTION AND MOLECULAR WEIGHT.

Jaken S, Black PH

Infectious Diseases Unit, Massachusettes General Hosp., Harvard Medical Sch., Boston, MA, 02118

J Cell Biol; 90(3):727-731 1981

The tumor promoter, phorbol myristate acetate (PMA), stimulates plasminogen activator production and extracellular release in confluent Swiss 3T3 cells. Coordinated with the increased extracellular release is a redistribution of the activity into plasma membrane-enriched fractions and a shi ft in the predominant mol wt species from 75,000 to 49,000 daltons. The evidence suggests that PMA induces the formation of the 49,000 dalton species which is preferentially located in plasma membrane-enriched fractions. (Author abstract) (19 Refs)

14. PHORBOL ESTER-INDUCED EXPRESSION OF PRIMATE RETROVIRUSES.

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Arch Geschwulstforsch; 51(7):615-622 1981

The 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced expression of simian retroviruses of type C (BaEV, SSV) or type D (MPMV) and of a type D isolate derived from a human cell line (PMFV) was studied in four human cell lines (Tu 197, HEK, E1, and A 204). TPA caused a significant but transient increase in the virus production and cytomorphological changes in the cell lines Tu 197, HEK, and E1, but not in A 204. The stimulation of the virus production reaches its max on days 2-3, at which time the virus production was 15-30x higher than in controls. The optimal TPA concentration was 5-10 nanog/ml. Higher and lower concentrations had a much weaker stimulating effect. (25 Refs) (In GER)

15. ENHANCEMENT OF EPSTEIN-BARR VIRUS-INDUCED TRANSFORMATION OF HUMAN LYMPHOCYTES BY TELEOCIDIN.

Hoshino H, Miwa M, Fujiki H, Sugimura T, Yamamoto H, Katsuki T, Hinuma Y

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Cancer Lett; 13(4):275-280 1981

The effect of teleocidin and 12-O-tetradecanoyl-phorbol-13-acetate (TPA) on Epstein-Barr virus (EBV)-induced transformation in human lymphocytes was examined. Human umbilical cord lymphocytes were infected with the B95-8 strain of EBV and cultured in soft agar. Teleocidin enhanced colony-forming efficiency approx 5x at 0.1 nanog/ml. TPA had a similar but lesser effect at the same concentration. Optimal concentrations were, respectively, 2.2 and 1.6 x 10(-10) M. Using the P3HR-1 EBV strain, which unlike strain B95-8 induces early antigen (EA) in C-6 lymphoblastoid cells after superinfection, the effects on plating efficiency were tested. The number of EA-positive cells as detected by immunofluorescence increased 2-3x in the presence of teleocidin or TPA. Cultures not infected with P3HR-1 produced less than 1% EA-positive cells even with teleocidin or TPA. Colony-forming efficiency of the newly transformed lymphoblastoid cells was 2x as great in the presence of 0.5 nanog/ml teleocidin as in its absence. TPA is known to have a similar effect. The evidence suggests that teleocidin and TPA act similarly to enhance the efficiency of

EBV infection of cord blood lymphocytes and also to stimulate colony formation of lymphocytes newly transformed by EBV. (19 Refs)

16. 12-O-TETRADECANOYLPHORBOL-13-ACETATE (TPA) TREATMENT ELEVATES THE NATURAL KILLER (NK) SENSITIVITY OF CERTAIN HUMAN LYMPHOID LINES.

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Cell Immunol; 63(2):237-248 1981

The natural killer (NK) sensitivity of two Epstein-Barr virus (EBV)-carrying Burkitt lymphoma lines (Daudi and Raji) and one EBV-negative lymphocytic leukemia-derived T-cell line (Molt-4) increased when they were cultured for 24 hr in the presence of the phorbol ester TPA. In the EBV-carrying lines, this increase occurred independently of the entry of the cells into the viral cycle. 12-O-Tetradecanoylphorbol-13-acetate (TPA)-treated Daudi and Molt-4 cells cross-competed for the effectors in the NK assay as indicated by the cold-target inhibition tests. TPA-treated cells showed an increased binding of human but not of mouse lymphocytes. (Author abstract) (19 Refs)

17. REGULATION OF GENE EXPRESSION BY TUMOR PROMOTERS. II. CONTROL OF CELL SHAPE AND DEVELOPMENTAL PROGRAMS FOR MACROPHAGES AND GRANULOCYTES IN HUMAN MYELOID LEUKEMIC CELLS.

Liebermann D, Hoffman-Liebermann B, Sachs L
Dept. Genetics, Weizmann Inst. Science, Rehovoth 76100, Israel
Int J Cancer; 28(3):285-291 1981

Regulation of the developmental programs for macrophages and granulocytes has been analyzed, using two-dimensional gel electrophoresis of the cytoplasmic protein changes, in a human myeloid leukemic cell line (HL60) that can be induced to differentiate to macrophages by the macrophage and granulocyte-inducing (MGI) protein and the tumor promoter 12-O-tetradecanoyl-phorbol-13-acetate (TPA), and to granulocytes by dimethylsulfoxide (DMSO). Studies on the protein changes induced by the different inducers showed a similar developmental program for macrophage differentiation induced by MGI or TPA, which differed from the beginning from the granulocyte program induced by DMSO. Comparison with normal cells from human peripheral blood has shown that the developmental programs induced in the HL60 cells are relevant to the normal programs of differentiation for these two cell types. Unlike MGI and DMSO, TPA induces rapid attachment of the HL60 cells to the surface of the Petri dish. Combined treatment with TPA and DMSO showed cell attachment, extensive spreading of the cells, the regulation of specific proteins and expression of the macrophage program. The addition of TPA to cells induced for the granulocyte program by DMSO resulted in cell attachment and spreading and a switch-over from the granulocyte to the macrophage program. The results indicate that cells in suspension can express either the macrophage or granulocyte program depending on the inducer, and that changes in cell shape associated with cell attachment induced by TPA can regulate specific proteins and restrict the developmental program to macrophages. It is suggested that the in v ivo environment of cells in relation to the possibilities for cell adhesion, which can be regulated by tumor promoters, may play a major role in determining the developmental program of myeloid and other cell types. (Author abstract) (41 Refs)

18. CHARACTERIZATION, BY IMMUNOPRECIPITATION, OF MYELOID- AND MONOCYTE-SPECIFIC ANTIGENS PRESENT ON THE HUMAN PROMYELOCYTIC CELL LINE (HL-60) IN THREE STAGES OF DIFFERENTIATION.

Mulder A, Alexander S, Engelfriet CP, Von dem Borne AE, Strominger JL
Dept. Immunohaematology, Central Lab. Netherlands Red Cross Blood Transfusion Service, Univ. Amsterdam, Amsterdam, The Netherlands
Proc Natl Acad Sci USA; 78(8):5091-5095 1981

The human promyelocytic leukemia cell line HL-60 is reactive with an antiserum raised against normal human granulocytes (AGS). Immunoprecipitation with AGS on [35S]methionine-labeled HL-60 cell lysates with subsequent analysis by NaDodSO4/polyacrylamide slab gel electrophoresis shows a major antigenic doublet with mol wt of 88,000 and 86,000, together with some minor antigens of lower mol wt. Upon stimulation with dimethyl sulfoxide or 12-O-tetradecanoylphorbol 13-acetate, which induces HL-60 to differentiate to mature granulocytes or monocytes/macrophages, respectively, this antigenic doublet disappears. 12-O-Tetradecanoylphorbol 13-acetate induces the synthesis of an antigen, mol wt 83,000, reactive with an antimonocyte serum. Neutrophil-specific alloantigens were not detected on HL-60 or its differentiated derivatives. (Author abstract) (29 Refs)

19. ACTIVATION OF THE METABOLISM OF THE FATTY ACYL GROUP IN GRANULOCYTE PHOSPHOLIPIDS BY PHORBOL MYRISTATE ACETATE.

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Biochim Biophys Acta; 665(3):491-497 1981

Phorbol myristate acetate is known to reproduce the stimulated oxidative activities characteristic of phagocytosis and its initial action is on the cell membrane. In the present study the effect of phorbol myristate acetate on the metabolism of the fatty acyl groups of granulocyte phospholipids was examined and compared with that of phagocytic stimuli. Phorbol myristate acetate stimulated the labeling of phosphatidylethanolamine, phosphatidylcholine and phosphatidylinositol by [1-14C]palmitic acid but not by [U-14C]glycerol, whereas starch granules selectively increased the labeling of phosphatidylinositol by both radioactive tracers. Labeled palmitic acid was found at both sn-1-and sn-2-positions of phospholipids and more radioactivity was recovered from the 2-position. The radioactivity at both positions was enhanced in stimulated cells. These data suggest that phorbol myristate acetate increased palmitic acid incorporation into glycerophospholipids by increasing the acylation of the lyso derivatives and that starch granules enhanced the formation of phosphatidylinositol via de novo synthesis and acylation of the lyso derivative as well. Both phorbol myristate acetate and starch granules selectively augmented the incorporation of [1-14C]arachidonic acid into phosphatidylinositol which exhibited the highest specific radioactivity among the phospholipids in control and in stimulated cells. The possible significance of the increased incorporation of arachidonic acid into phosphatidylinositol is discussed. (Author abstract) (24 Refs)

ANTICARCINOGENESIS BY CHEMICAL AGENTS

20. ENHANCEMENT OF TUMOR FORMATION IN MOUSE LUNG BY DIETARY BUTYLATED HYDROXYTOLUENE.

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Toxicology; 21(2):95-104 1981

The effect of three antioxidants, butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), and ethoxyquin (EQ) on the incidence of urethan-induced lung tumors in male A/J mice was investigated. The test diet containing 0.75% BHT, 0.75% BHA, or 0.75% EQ was given 1 day/wk for 8 wk beginning 1 wk after a single ip injection of urethan (500 or 250 mg/kg body wt).When sacrificed 4 mo after urethan treatment, the BHT-treated mice had a significantly higher multiplicity of tumors (p less than 0.05) than did the animals given urethan alone or urethan followed by BHA or EQ, at both urethan concentrations. A positive control group given 500 mg/kg urethan followed 1 wk later by ip injections of 300 mg/kg BHT in corn oil 1 x/wk for 8 wk had a tumor incidence comparable to that induced by urethan and po BHT, showing that route of administration of BHT is irrelevant with regard to tumor enhancement. When test diet containing 0.75% BHT or 0.75% BHA was given continuously for 8 wk immediately following a single ip injection of 500 or 250 mg/kg urethan and the animals were sacrificed 4 mo after urethan treatment, the BHT-treated mice again had a significantly higher multiplicity of tumors (p less than 0.05) compared with animals given urethan alone or urethan and BHA. When test animals were fed ad libitum for 2 wk such that they ingested an av of 180 mg BHT or 187 mg BHA, then injected with 1,000 mg/kg urethan and sacrificed 4 mo later, the tumor incidence in the BHT-treated animals was similar to that in controls, while BHA pretreatment significantly reduced (p less than 0.05) the tumor incidence. Histologic classification showed that BHT treatment did not alter the types or ratios of tumors induced by urethan. It appears that the use of BHT as a food additive should be reevaluated. (18 Refs)

21. EFFECTS OF 2-AND 3-TERT-BUTYL-4-HYDROXYANISOLE ON GLUTATHIONE S-TRANSFERASE AND EPOXIDE HYDROLASE ACTIVITIES AND SULFHYDRYL LEVELS IN LIVER AND FORESTOMACH OF MICE.

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Cancer Res; 41(10):3940-3943 1981

Butylated hydroxyanisole, a food additive, has been found to inhibit the neoplastic effects of a wide variety of chemical carcinogens. The commercially available preparations of butylated hydroxyanisole contain two isomers, 2-tert-butyl-4-hydroxyanisole (2-BHA) and 3-tert-butyl-4-hydroxyanisole (3-BHA). Both isomers induce increased activities of glutathione (GSH) S-transferase and epoxide hydrolase and increase acid-soluble sulfhydryl concentration in hepatic and forestomach tissues of A/HeJ mice. The inductions were assayed after 2 wk of feeding diets containing the two isomers. 3-BHA induced an increase in the activity of hepatic microsomal epoxide hydrolase by 1.4x that of the control. The activity of cytosol GSH S-transferase was enhanced by both isomers. In the liver, the 3-BHA induction was more than 3x higher than that of 2-BHA. In the forestomach, however, the induction effect of the two isomers was reversed. The overall magnitude of the induction was much lower in the forestomach than in the liver. Synergistic effects on the induction of GSH S-transferase activity were observed in the forestomach cytosol when mixtures of different proportions of the two isomers were added to the diet. Max enzyme activity was obtained at a ratio of 75% 2-BHA and 25% 3-BHA. No synergistic effect was observed with the corresponding hepatic cytosolic enzyme. The relative inductive effects of 2-and 3-BHA on the acid-soluble sulfhydryl level of liver and forestomach tissues followed closely those on GSH S-transferase activity. The results of the present study show that the two isomers of butylated hydroxyanisole differ in the magnitude of their effects on carcinogen-metabolizing systems of the liver and forestomach. (Author abstract) (27 Refs)

22. SEX DIFFERENCES IN THE EFFECTS OF RETINOIDS ON CARCINOGENESIS BY N-NITROSOBIS(2-OXOPROPYL)AMINE IN SYRIAN HAMSTERS.

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Cancer Lett; 14(1):13-21 1981

Male and female Syrian hamsters received a single dose of N-nitrosobis(2-oxopropyl)amine (BOP: 40 mg/kg, sc) and 1 wk later were fed one of four retinoid types (13-cis-retinoic acid (13-cis-RA), N-ethylretinamide (ERA), 2-hydroxy-ethylretinamide (OH-ERA), or 4-hydroxyphenylretinamide (PRA)) each at three dose levels reported as 0.05, 0.1, and 0.2 milliM/kg diet. The wt of the pancreas was influenced by the sex and retinoid level: wt increased in females fed the high retinoid level and decreased in males fed the 0.1 milliM level. Nearly all animals developed pancreatic adenomas. The av number of adenomas was reduced in female hamsters fed retinoids. The greatest decrease occurred with 13-cis-RA (48% reduction), with reductions intermediate for ERA and OH-ERA (39%), and smallest for PRA (14%). In male hamsters, pancreatic adenoma incidence was not influenced by retinoid treatment; however, the multiplicity of these lesions in males fed OH-ERA and PRA was greater than those fed 13-cis-RA, ERA, or control diet. The pancreatic carcinoma incidence was not influenced by retinoids, although female hamsters fed 13-cis-RA developed fewer carcinomas per animal than did animals fed ERA. In female, but not male, hamsters, the liver tumor incidence was reduced from 60% to 21% by feeding OH-ERA, and the gallbladder tumor incidence from 60% to less than 10% in females fed 13-cis-ERA and ERA. These results suggest that sex hormones or other sex differences may influence the factors which determine the ability of retinoids to inhibit carcinogenesis. (33 Refs)

23. INHIBITION OF DMBA CARCINOGENESIS OF HAMSTER BUCCAL POUCH BY PHENANTHRENE AND DIMETHYLNAPHTHALENE.

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Carcinogenesis; 2(8):723-729 1981

Eighty male and female young adult golden Syrian hamsters were divided into four groups. Group A was the control group. Groups B, C, and D were treated by painting of the left buccal pouch three times per wk. Group B was painted with a 0.5% soln of 7,12-dimethylbenz[a]anthracene (DMBA) in heavy mineral oil. Group C was painted with mineral oil con-

taining 0.3% 1,4-dimethylnaphthalene (DMN) and 0.5% DMBA. Group D was painted with mineral oil containing 0.3% phenanthrene (Phe) and 0.5% DMBA. Rats from each group were sacrificed at 8, 10, 12, 14, and 16 wk. The buccal pouches, heart, lungs, liver, spleen, kidneys, and adrenals were studied. Group A showed no tumors. Group B showed early invasive carcinoma of the buccal pouch with ulcerations. Group D showed significant reduction in the number of tumors and in tumor size over group B, without ulceration. Group C showed intermediate tumor numbers and sizes. Apparently Phe, and to a lesser extent DMN, retard the development of epidermoid carcinomas in hamster buccal pouches induced by DMBA. (35 Refs)

MODIFICATION BY DIETARY FACTORS

24. EFFECT OF PRETREATMENT WITH PREGNENOLONE-16ALPHA-CARBONITRILE AND PROTEIN-FREE DIET ON THE METABOLISM AND CARCINOGENICITY OF DIMETHYLNITROSAMINE.

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Pathologische Institut, Universitat Freiburg, 78 Freiburg, W. Germany
Carcinogenesis; 2(8):757-761 1981

Adult female Wistar rats were pretreated with a protein-free diet (PFD), pregnenolone-16alpha-carbonitrile (PCN: total dose 25 mg, 5 equal doses at 12-hr intervals), or a combination of both. Rats from each group were given a single injection of 60 mg dimethylnitrosamine (DMN). PCN-pretreated rats showed a 50% tumor incidence after a mean survival time of 672 days. PFD (30 rats) and PFD + PCN (2 8 rats) groups showed a tumor incidence of 83-85% and a mean survival time of 357 and 396 days. Rats treated only with PCN showed a tumor incidence of 50% with a mean survival time of 805 days. The incidence of neoplasms, particularly cholangiomas, was highest following treatment with PCN only. The PFD and PFD + PCN groups showed lower incidence of cystic cholangiomas and no malignant liver tumors. Methylation of liver DNA purines by a single dose of [14C] DMN was greatest in the PCN and PFD groups and lower in the PFD + PCN group. Methylation of renal DNA was highest in the PFD and PFD + PCN groups and lower in the PCN-only pretreated group. Differences in lung tissue were smaller among the various groups. Both PCN and PFD reduced the hepatotoxicity of DMN. PCN had no effect on the induction of renal tumors. Apparently PCN does not cause a reduction in DNM metabolism in the liver and the resultant increase in DNA methylation in the kidney. PFD shifts the metabolism of DMN from the liver to the kidney, lowering the carcinogenic effect of DMN in the liver and raising it in the kidney. (24 Refs)

25. PROMOTION BY UNSATURATED FAT OF AZASERINE-INDUCED PANCREATIC CARCINOGENESIS IN THE RAT.

Roebuck BD, Yager JD, Longnecker DS, Wilpone SA
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Cancer Res; 41(10):3961-3966 1981

Diet has been shown to modulate the incidence of a wide variety of chemically induced cancers in animals. Various diets fed either during the initiation stage or the postinitiation (promotion) stage of carcinogenesis were evaluated for their ability to modulate the incidence of pancreatic cancer. Male Wistar/Lewis rats were treated with multiple injections of the pancreatic carcinogen, azaserine, during a 6-to 7-wk-long initiation phase and were autopsied after a postinitiation phase of 34 or 44 wk. The following diets were evaluated for their effects on the incidence of pancreatic neoplasms during each stage of carcinogenesis: high saturated fat; two high unsaturated fats (corn oil and safflower oil); low protein; and caloric restricted. A purified control diet was fed during that stage when the test diets were not fed. The incidence of pancreatic adenomas and adenocarcinomas was evaluated by light microscopy. Feeding of the caloric-restricted diet during the initiation phase suppressed the pancreatic neoplasm incidence. None of the other diets tested had an effect on the incidence of pancreatic cancer during the initiation phase. During the postinitiation phase, both high-unsaturated-fat diets but not the high-saturated-fat diet significantly elevated the pancreatic neoplasm incidence. The low-protein and caloric-restricted diets had no effect on the neoplasm incidence when fed during the postinitiation phase. Thus, diets high in unsaturated fat appear to promote pancreatic carcinogenesis in the azaserine-treated rat while a diet high in saturated fat failed to show a similar degree of enhancement of pancreatic carcinogenesis. (Author abstract) (42 Refs)

26. COMPARISON OF THE MUTAGENICITY OF THE DIET IN RELATION TO MORTALITY FROM GASTRIC CANCER. II. MUTAGENICITY OF THE FOODS INGESTED BY THE INHABITANTS OF THE COUNTRYSIDE OF NARA AND KAGOSHIMA (MEETING ABSTRACT).

Michioka I, Kamiyama S
Dept. Hygiene, Akita Univ., Sch. Medicine, Hondo, Akita 010, Japan
Nippon Eiseigaku Zasshi; 36(1):178 1981

Foods to be consumed by the inhabitants of the villages in Haibara-machi, Nara Prefecture, and Togo-cho, Kagoshima Prefecture, which have different mortalities from gastric cancer, were frozen and air-mailed to this facility where they were thawed and the mutagenicity of the acetone-soluble fraction of the ether:petroleum ether (1:1) extract of the homogenate of the edible part was determined by the Ames' method with Salmonella typhimurium TA100. The foods with a relative mutagenicity rate of less than 1.5, 1.5-3.0 and more than 3.0 in the extract were designated negative, false-positive and positive, respectively. The rate of ingestion of negative and positive foods was strongly related to the mutagenicity of the foods for Akita and Iwate. However, in Nara the positive mutagenicity rate was low compared to that of gastric cancer mortality, which was high. The presence of some factors which promote the action of the mutagenic substances in foods on the gastric epithelium was thought to be responsible for the incidence of gastric cancer in Nara. (no Refs) (In JPN)

27. DIETARY SELENIUM INTAKE AND GROWTH OF THE MT-W9B TRANSPLANTABLE RAT MAMMARY TUMOR.

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Dept. Breast Surgery, Roswell Park Memorial Inst., Buffalo, NY, 14263
Cancer Lett; 14(1):101-107 1981

The effect of dietary selenium deficiency and supplementation on the growth of the transplantable MT-W9B mammary carcinoma in syngeneic Wistar-Furth female rats was investigated. The rats were fed a high fat diet (25% corn oil) supplemented with either less than 0.02 ppm, 0.1 ppm, or 2 ppm sele-

nium. Selenium deficiency caused a drastic reduction in the activity of hepatic glutathione peroxidase, while excess selenium had little effect on its activity. Palpable tumors appeared earlier in the rats given less than 0.02 ppm or 0.1 ppm selenium, compared to those given 2 ppm. Dietary selenium at 2 ppm reduced the tumor wt by approx 50% compared to that in the 0.1 ppm group. No histological change in the tumors accompanied with the wt decrease. It is suggested that the inhibitory effect of selenium is selective, without inducing any wt loss or any recognizable toxicity in the animals. (25 Refs)

MODIFICATION BY HORMONAL FACTORS

28. INHIBITION OF DNA SYNTHESIS IN MOUSE EPIDERMIS AND BREAST EPITHELIUM BY DEHYDROE PIANDROSTERONE AND RELATED STEROIDS.

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Carcinogenesis; 2(8):717-721 1981

Male ICR mice and female virgin C3H-A/A mice were treated with dehydroepiandrosterone (DHEA), DHEA-sulfate, DHEA-sulfatide, 16alpha-Br-epiandrosterone (Br-Epi), estradiol-17beta, progesterone, testosterone, or corticosterone. The activity of glucose-6-phosphate dehydrogenase (G6PDH) and the level of incorporation of [3H]thymidine in male mouse epidermis was determined. Incorporation of [3H]thymidine was also measured in female mouse breast epithelium. DHEA and DHEA-sulfatide significantly inhibited G6PDH activity in the epidermis. DHEA-sulfate had no inhibitory effect. Br-Epi was the most active inhibitor of the steroids tested. DHEA and DHEA-sulfatide inhibited the stimulation of [3H]thymidine incorporation by 12-O-tetradecanoylphorbol-13-acetate (TPA) in mouse epidermis. DHEA-sulfate did not have this effect. Br-Epi was much more potent an inhibitor in both the epidermis and breast epithelium than DHEA. Of the sex steroids tested, only corticosterone inhibited TPA-stimulated incorporation of [3H]thymidine. The results indicate that the activity of DHEA, which has been shown to suppress spontaneous breast cancer development in mice, is not limited to breast epithelium. A possible relationship to spontaneous breast cancer in humans is suggested. (25 Refs)

29. INFLUENCE OF THE ESTROUS CYCLE DURING CARCINOGEN EXPOSURE ON NITROSOMETHYLUREA-INDUCED RAT MAMMARY CARCINOMA.

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Cancer Res; 41(10):3857-3862 1981

The influence of individual stages of the rat estrous cycle during exposure to l-nitroso-l-methylurea (NMU) on mammary tumor incidence, latency, number, and cytosol receptor dynamics for estrogen and progesterone was determined. Virgin female Buffalo rats were separated into three groups on day 53 according to their vaginal smear pattern. NMU (5 mg/100 g body wt, iv) was administered in 3 mo doses beginning at 53 to 55 days of age on diestrus, proestrus, or estrus between 9:00 and 11:00 a.m. Groups of rats had their second and third injections of NMU on the same day of the estrous cycle as their initial injection. All animals were killed during the morning on a diestrus day. Receptors for estrogen and progesterone were determined by a modified dextran-coated charcoal method and by sucrose density gradient analysis. Mean latencies to first tumor appearance in diestrus, proestrus, and estrus groups were 104.4, 83.6, and 91.4 days, respectively (p less than 0.05, diestrus versus estrus and proestrus) following the NMU injection. The mean number of tumors per rat was significantly higher in rats injected on proestrus (4.5) or estrus (4.3) than on diestrus (2.0). Estradiol bound to receptor sedimented at 8 and 4 s and was suppressed by diethylstilbestrol and estradiol. Progesterone receptor migrated to 7.8 and 4 s regions. Estrogen receptor incidence (100%) and content (16.7 fmol/mg cytosol protein) was highest in rats injected on diestrus. In the proestrus and estrus injected groups, estrogen receptor incidence was 95 and 63% and content was 10.2 and 11.2 fmol/mg protein, respectively. The affinity of estradiol for its receptor was not significantly altered in any group. Although there were no statistically significant differences in progesterone receptor incidence or affinity between groups, progesterone receptor content (74.6 fmol/mg cytosol protein) was significantly higher in tumors from rats injected on proestrus than on diestrus. These data suggest that the prevailing hormonal milieu of the estrous cycle during NMU exposure may be critically important to the subsequent biological behavior and steroid receptor status of carcinogen-induced rat mammary tumors. (Author abstract) (41 Refs)

30. HORMONAL INDUCTION OF KIDNEY TUMOURS IN MALE HAMSTERS. INHIBITION OF GROWTH BY A PHENOTHIAZINE DERIVATIVE (PERPHENAZINE).

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Eur J Cancer Clin Oncol; 17(7):767-773 1981

Experiments have shown that long-term treatment of male hamsters with estrogen will cause renal carcinomas, neoplastic changes in the pars intermedia of the pituitary and highly elevated levels of melanocyte-stimulating hormone (MSH). To test if MSH was fundamentally involved in renal carcinogenesis, a group of hamsters was treated for 317 days with perphenazine which is known to elevate MSH levels. A second group was treated with estrogen while a third received a combination of estrogen and perphenazine for a similar period of time. Serum MSH levels were significantly elevated in the perphenazine group but kidney tumors were absent. All estrogen-treated animals developed kidney tumors but only 19% of those given the combined treatment developed kidney tumors despite highly elevated levels of MSH. The findings suggest that MSH does not play a significant role in renal carcinogenesis in the hamster. Perphenazine may inhibit the induction of estrogen-induced tumors by competing with estrogen for receptors in the kidney or may protect cells from toxic injury by stabilizing cell and microsomal membranes. The phenothiazines are known to induce, and increase the activity of, microsomal enzymes and that may lead to enhanced detoxification of the carcinogen. Other effects of phenothiazines include elevation of prolactin levels. The fact that the body wt of animals treated with DES and perphenazine was significantly lower than that o f the other groups may indicate that the reduction in tumor incidence was the result of a certain degree of undernutrition. Further work is required to elucidate the mechanism of tumor inhibition by phenothiazine derivatives. (Author abstract) (32 Refs)

MODIFICATION BY GENETIC FACTORS

31. HEREDITARY AND ENVIRONMENTAL FACTORS IN THE CAUSATION OF NEOPLASIA BASED ON STUDIES IN XIPHOPHORUS.

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Klin Wochenschr; 59(17):943-956 1981

The genetic information for neoplastic transformation is inherited as a normal part of the genome in all individuals of Xiphophorus. Neoplasia, however, was found only in hybrids between members of different populations and local races. It can be classified in (a) a large group that is triggered by mutagens, (b) a large group triggered by promoters, (c) a small group that develops 'spontaneously', and (d) a small group that is inherited according to Mendelian Laws. The process leading to susceptibility for neoplasia is represented by the disintegration of coadapted gene systems that normally protect the fish from neoplasia. Hybridization is the most effective process that leads to disintegration of the protection gene-systems. Environmental mutagens and promoters (ie carcinogens) may complete disintegration and thus may trigger neoplasia. The phenomenon of introducing susceptibility to neoplasia by means of hybridization has been observed in a large variety of plants and animals. While we have no data on the relation between hybridization and cancer in human beings comparable to those in plants and animals, we put the question whether the many facts on tumor incidence in humans, that do not agree with the concept of the primacy of environmental factors in carcinogenesis may be explained by interpopulational and interracial hybridization in preceding generations. Based on our studies on Xiphophorus we suppose that environmental factors represent only the peak of an iceberg in the multistep process of the causation of neoplasia. The most important steps leading to neoplasia, ie those that bring about susceptibility, are supposed to be hidden in our ancestry. (Author abstract) (87 Refs) (In GER)

MODIFICATION BY VIRUSES, IMMUNE FACTORS OR IRRADIATION

32. INHIBITION OF ADENOVIRUS-TRANSFORMED CELL ONCOGENICITY BY ADENO-ASSOCIATED VIRUS.

Ostrove JM, Duckworth DH, Berns KI
Dept. Microbiology, Johns Hopkins Univ., Sch. Medicine, Baltimore, MD, 21205
Virology; 113(2):521-533 1981

Adeno-associated virus (AAV) has been shown to inhibit the oncogenicity and transforming ability of adenovirus (Ad). Using the H14b Ad-transformed hamster cell line, we have developed a model system in which to characterize the molecular events responsible for these inhibitory effects. A AV infection of H14b cells decreases their oncogenicity by approx threefold. The tumors that do arise are significantly smaller and have a longer latent period. AAV infection also alters the in vitro properties of the H14b cells, reducing cloning efficiency in methyl cellulose by 38-92% and saturation density by two- to four-fold. The molecular basis of this inhibition appears to be an inhibition of production of the 58K tumor antigen as determined by fluorescent antibody and immunoprecipitation studies. The reduction in the levels of tumor antigens are not due to alterations or loss of the Ad genome within H14b cells but may reflect an alteration in transcription or processing of Ad-specific mRNA. AAV infection of H14b cells does not lead to detectable levels of AAV DNA synthesis, but some AAV transcripts are made. This is the first instance in which AAV transcription has been detected in an Ad-transformed cell line. (Author abstract) (42 Refs)

33. COCARCINOGENIC EFFECT OF VACCINIA VIRUS AND HERPES SIMPLEX VIRUS IN TISSUE CULTURE.

Mazurenko NP, Merekalova ZI, Pavlish OA, Bykovskii AF, Kurtsman MIa, Mazurenko NN
All-Union Cancer Res. Center, Moscow, USSR
Vestn Akad Med Nauk SSSR; (7):3-10 1981

Cocarcinogenic effect of vaccinia virus (VV) and herpes simplex virus (HSV) was studied in transplantable murine cell lines. The cultured cells of embryonal tissue of BALB/c mice were infected with VV, and the expression of structural protein p30 was assayed by indirect immunofluorescence reaction. Specific cytoplasmatic fluorescence was recorded in 15-20% of cells. Max fluorescence was observed 48-72 hr after infection, which corresponded to the onset of Rauscher leukemia virus replication. HSV-2 caused malignant transformation of BALB/3T3 cells. Inoculation of irradiated BALC/c mice with transformed cells (subclones 333-0 and 333-1) produced tumors in 25% and 80% of the animals. Transformed cells expressed the endogenous murine retrovirus Type 3. (29 Refs) (In RUS)

34. THE EFFECT OF PHENFORMIN, L-DOPA AND PARACHLOROPHENYLALANINE TREATMENT OF IMMUNE RESPONSE AND CHEMICAL CARCINOGENESIS DEVELOPMENT IN BALB/C MICE.

Vinnitsky VB, Yakimenko VA
R. E. Kavetsky Inst. Oncology of Acad. Science of Ukrainian SSR, Kiev, USSR
Vopr Onkol; 27(6):45-50 1981

Treatment with 20-methylcholanthrene resulted in the increase in hypothalamic levels of noradrenaline and serotonin in BALB/c mice. Immunization of carcinogen-treated animals with ovine RBCs was followed by changes in the hypothalamic levels of central neurotransmitters, opposite to those in intact immunized controls. After correction of the levels of neurotransmitters in the hypothalamus with phenformin, parachlorophenylalanine or L-dopa carried out prior to immunization, the fraction of antibody-producing cells in the spleen of carcinogen-treated mice returned to normal. A combined administration of immunostimulators and drugs for correction of hypothalamic levels of noradrenaline and serotonin potentiated inhibitory effect of the former on chemical carcinogenesis. (Author abstract) (15 Refs) (In RUS)

OTHER RELATED STUDIES

35. MANIFESTATION OF CARCINOGENESIS AS A STOCHASTIC PROCESS ON THE BASIS OF AN ALTERED MITOCHONDRIAL GENOME.

Neubert D, Hopfenmuller W, Fuchs G
Institut fur Toxicologie und Embryopharmakologie, Freien Universitat Berlin, Garystrasse 9, D-1000 Berlin 33, W. Germany
Arch Toxicol; 48(2/3):89-125 1981

Computer calculations are used to show the feasibility of a concept which explains the manifestation of a pathological cell function from a latent state by the phenomenon of extrachromosomal inheritance (through the mitochondrial genome) in mammalian cells. A hypothesis is submitted in which this principle is applied to the process of carcinogenesis. According to this concept, the manifestation of a tumor cell - after the initiation stage - entirely depends on stochastic events, ie, random distribution of mitochondria during cell divisions, with an accumulation of the lesion in a few out of many cells. We feel that this concept comprises a better explanation of many characteristics and peculiarities of the phenomenon of carcinogenesis than do attempts which explain tumor formation as a phenomenon caused by mutation in a nuclear genome. A consideration of the principles presented automatically leads to a number of specific consequences with regard to carcinogenesis. Some of these consequences are discussed. They include: 1. the process of malignant transformation should not be irreversible for all the cells of a progeny; 2. the number of mitochondria in a cell type should be inversely correlated to tumor frequency; 3. the latent period should mainly be determined by the cell division rate and the 'extent' of the initiating event; 4. susceptibility to carcinogenesis may be substantially higher if the number of mitochondria per cell line is increasing or decreasing, ie, during the embryonic and fetal periods; 5. heterogeneous types of cells may arise from a single 'initiated' cell, and 6. the process of malignant transformation should not necessarily be confined to one generation of the species. In addition, experimental approaches to support the submitted concept are suggested. (Author abstract) (91 Refs)

36. LARYNGEAL CANCER: AN EXPLANATION FOR THE APPARENT OCCUPATIONAL ASSOCIATION.

Chovil A
216 Northwood Drive, Willowdale, Ontario M2M 2K4, Canada
Med Hypotheses; 7(7):951-956 1981

The hypothesis that laryngeal cancer occurs as a result of exposure of the larynx to lipid soluble carcinogenic agents that can penetrate the squamous epithelial covering is proposed. Alcohol and vocal abuse may have promoting effects. In the presence of concomitant carcinogenic exposure , the changes may progress to keratoses and ultimately to premalignant or malignant states. (22 Refs)

37. A NEW VIEW OF THE ETIOLOGY OF NASOPHARYNGEAL CARCINOMA.

Hirayama T, Ito Y
(c/o Ito) Dept. Microbiology, Faculty Medicine, Kyoto Univ., Kyoto 606, Japan
Prev Med; 10(5):614-622 1981

Epidemiological studies showed a high incidence of nasopharyngeal carcinoma (NPC) in southern regions of China. Also found in these regions are plants of the Euphorbiaceae family, including Croton tiglium (the source of croton oil) and other species used as herbal drugs. Interaction of herbal drugs and anti-Epstein-Barr virus (EBV) titers was noted. Use of the herbal drugs was related to nasal infection by microbes such as Fusobacterium. The combined effects of drug use and EBV induction were synergistic rather than additive. Fusobacteria in culture produced n-butyric acid, which had a low, but definite EBV-inducing activity in human lymphoblastoid P3HR-1 cells. Combined treatment with nanog concentrations of croton oil and n-butyrate produced marked increase in EBV antigens in EBV genome-carrying P3HR-1 and Raji cells. Apparently EBV is induced and activated by the combination of bacterial fatty acid and herbal oils. It is suggested that the activated EBV then initiates steps resulting in NPC. (33 Refs)

38. EFFECT OF MAJOR SMALL BOWEL RESECTION ON DIMETHYLHYDRAZINE-INDUCED BOWEL CARCINOGENESIS.

Harte PJ, Steele G, Rayner AA, Munroe AE, King VP, Wilson RE (c/o Steel) Brigham and Women's Hosp., 75 Francis St., Boston, MA, 021151
J Surg Oncol; 18(1):87-93 1981

We have investigated the effect of distal small bowel resection on chemically induced tumors of the gastrointestinal tract in Wistar/Furth (W/Fu) rats. Dimethylhydrazine (DMH) (20 mg/kg sc once wk x 16) was commenced 3 mo after rats underwent resection of the distal 30 cm of small bowel (1/3 resection) or after sham small bowel resection (controls). Fifty wk after the start of DMH administration, tumors were found in 15 of 25 animals who underwent small bowel resection compared to 9 of 31 animals in the control group (p less than 0.05). After small bowel resection, 8 of 15 tumors occurred at the site of anastomosis but no anastomotic tumors were seen after sham resection. In addition, tumors were larger and more invasive after small bowel resection. These data indicate that major small bowel resection potentiates DMH induced-intestinal carcinogenesis. (Author abstract) (28 Refs)

REVIEWS

39. TWO INDEPENDENT ASPECTS OF TUMOR PROMOTION.

Berenblum I, Armuth V
Weizmann Inst. Science, Rehovot, Israel
Biochim Biophys Acta; 651(1):51-63 1981

The possibility of separate and independent mechanisms of tumor promotion is explored based on a review of evidence for sites of action within the cell. The multi-stage theory of carcinog enesis is presented. Evidence for two types of promoting action is discussed: that operating at the regulator-gene level and that operating at the level of the cell-surface membrane. Tumor promotion is generally regarded as an epigenetic phenomenon in an initiated cell which permits the phenotypic expression of an altered genotype. Since an influence on the cell's mutation rate or its repair mechanisms would need to operate close in time to initiation, these mechanisms are not widely regarded as likely. Growing evidence suggests that promotion may proceed by the derepression of a neighboring regulator gene brought about by the action of some newly synthesized tumor-specific protein(s). Cell membranes in general and cell-surface membranes in particular have an important role in regulating cellular functions, and a great variety of changes in cell-surface membranes is known to effective in this regard.

Lack of cell adhesiveness and of contact inhibition in neoplastic cells have long been recognized as cell-surface phenomena. There is evidence that promoters, particularly phorbol ester promoters, can bind to cell-surface membranes and alter their properties. Induction of plasminogen activator, prostaglandins, enzymes of polyamine biosynthesis, and alterations in cyclic nucleotide levels are known cytoplasmic effects of promoter action. Implications and interrelations of these findings are discussed. (224 Refs)

40. INDUSTRIAL CARCINOGENESIS.

Vickers CF
Dept. Dermatology, Univ. Liverpool, Liverpool L69 3BX, England
Br J Dermatol; 105(Suppl21):57-61 1981

The occurrence of carcinogens in the workplace, particularly as they relate to skin cancers, is reviewed. Such carcinogens include coal, tar, paraffin oil, lubricating oil, pitch, and creosote. Arsenic contamination in the air and water results from metallurgical processe. Arsenic also occurs in dyes, fruitsprays, glass, and various other materials. X-rays, UV, and other electromagnetic radiation are carcinogenic. Single incidents of trauma can be accepted on a legal basis as carcinogenic, although they are more likely co-carcinogenic. Cutaneous carcinomas seem to require the interaction of a carcinogen and a co-carcinogen, such as UV or trauma, more than do organspecific carcinomas. The applications of the British system of compensation in cases of exposure to carcinogens is discussed. (14 Refs)

41. CELL-MATRIX INTERACTIONS IN DEVELOPMENT AND NEOPLASIA.

Ruoslahti E
La Jolla Cancer Res. Foundation, 2945 Science Park Road, La Jolla, CA, 92037
Oncodev Biol Med; 2(4):295-303 1981

A review of cell-matrix interactions is presented. It is now commonly believed that cells communicate with the extracellular matrix that surrounds them and that this communication influences differentiation. Significant progress was recently made in understanding the chemistry of the ext racellular and basement membrane macromolecules, including collagens, fibronectin, and laminin. Attachment of cells to component macromolecules of extracellular matrixes has been used as an indicator of a primary interaction of cells with extracellular matrix; these interactions may subsequently lead to changes in gene expression in adherent cells. Cells plated on dishes coated with fibronectin attach and spread rapidly; the actual function of fibronectin is not known, but it mediates the attachment of most types of cells, promotes cell motility, prevents fusion of myoblasts and differentiation of chondrocytes, and acts as an opsonin in plasma. Laminin also appears to promote cell attachment, but with a more restricted specificity than fibronectin. Fibronectin and other proteins mediate the attachment of cells to collagen. Fibronectin may play a role in directing differentiation and morphogenetic movements in certain cells. Laminin may be involved in tissue organization, cell proliferation, and differentiation. Transformed cells have greatly reduced amounts of fibronectin on their surfaces and reduced amounts of collagen production. Laminin in malignant cells has not yet been well studied. The possible importance of altered cell-matrix interactions in tumorigenesis are discussed. (68 Refs)

42. MECHANISMS OF MALIGNANT GROWTH.

Grundmann E
Pathologisches Institut, Universitat Munster, Domagkstrasse 17, D-4400 Munster, W. Germany
Klin Wochenschr; 59(17):931-941 1981

Analysis of invasive malignancy focuses on the particularly high growth rate of tumor cells, and on the aggressive mechanisms of histolysis favoring the infiltration of the malignant cells into the surrounding tissue. Specific significance is attributed to a certain enzyme directed against Type IV collagen, and to the auto-locomotion of tumor cells, properties that may also explain the highest selective process of metastasization in at least three consecutive steps: Tumor cells invade a blood or lymph vessel, they are transported along blood or lymphatic pathways, and they eventually infiltrate foreign tissue after penetration and destruction of blood or lymph vessel walls. Among the factors involved in the process of metastasization, special interest is due to blood coagulation and to the coexistence of different tumor cell subpopulations within a primary. These features of malignant growth are based on the loss of functional differentiation as manifested eg in the loss of tissue-specific nuclear chromatin structures. Tumor development is triggered by the so-called primary factors which always affect the DNA, ie, the cell genome. Chemical carcinogens, viruses, and shortwave or ionizing irradiation induce DNA defects which, however, will be reversed and mended by special repair mechanisms in most cases. Thus, the actual development and spread of malignancy is ultimately due to deficient repair. Co-factors favoring and promoting carcinogenesis may shorten the latency period, among several other specific chemicals and hormones. Based on current knowledge of tumor dormancy a new concept is proposed for the chronological and morphological sequence of carcinogenesis: Following the development of a primary tumor, certain as yet undefined growth factors and especially immunological factors may be responsible for the development of a progressive tumor disease. (Author abstract) (62 Refs) (In GER)

43. FACTORS STIMULATING AND INHIBITING TUMOR GROWTH IN CARCINOGENESIS.

Kochergina NI, Kosova IP
Res. Lab. Experimental Immunobiology, Moscow, USSR
Usp Sovrem Biol; 91(3):409-418 1981

Literature data on tumor factors that can stimulate or inhibit proliferation of normal or neoplastic cells are reviewed. Factors isolated from murine sarcoma 180, spontaneous and explanted murine mammary gland carcinomas, tissue-specific inhibitors of cell divisions (chalones), and polysomal RNA from Rous sarcoma cells were found to regulate the neoplastic growth and to affect tumor transplantability. Tumor factors were shown to inhibit the antibody formation. The sera of cancer patients was shown to contain factors that inhibited lymphocyte cytotoxicity. In response to stimulation with tumor antigens, T lymphocytes formed the clone of killer cells. The degree of lymphocyte transformation depended upon the ratio of lymphocytes and tumor antigen. Tumor factors were found to inhibit not only the antitumor but also the transplacental immunity. Stimulation of tumor antigenicity can stimulate the immune system of tumor-bearing organism and thus can have an immunotherapeutic effect. (108 Refs) (In RUS)

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1. TOXICOLOGICAL ASPECTS OF POLYCYCLIC AROMATIC HYDROCARBONS (PAH).
De Fernicola NA, De Azevedo FA
Divisao de Toxicologia e Ecotoxicologia, Diretoria de Tecnologia e Desenvolvimento, Sao Paulo, Brazil
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MODIFICATION OF CARCINOGENESIS

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Cancer Genet Cytogenet; 4(1):69-88 1981

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3173/2:

TUMOR PROMOTION AND COCARCINOGENESIS IN MOUSE SKIN

1. BIOCHEMICAL MECHANISM OF MODULATION OF SKIN CARCINOGENESIS BY RETINOIDS.

Verma AK
McArdle Lab. for Cancer Res., Univ. Wisconsin Medical Center, Madison, WI, 53706
Retinoids: Advances in Basic Research and Therapy, Proceedings of the International Dermatology Symposium held in Berlin, W. Germany, 13-15 October, 1980. Orfanos CE, Braun-Falco O, Farber EM, Grupper C, Polano MK, and Schuppli R, ed. Berlin, Springer-Verlag, 527 pp., 1981.

Investigations of mechanisms involving retinoids in the two-stage model of mouse skin carcinogenesis are reviewed. Application of retinoic acid (RA) 1 hr before application of 12-O-tetradecanoylphorbol-13-acetate (TPA) led to inhibition of induction of ornithine decarboxylase (ODC) and resultant putrescine accumulation, and inhibition of enhanced DNA synthesis at 18 hr, but not at 24 or 48 hr. RA did not inhibit S-adenosylmethionine decarboxylase induction, incorporation of [3H]leucine or [3H]histidine into epidermal protein, induction of cyclic AMP phosphodiesterase activity, accumulation of prostaglandins E and F, or hyperplasia occurring 1 or 3 days after TPA treatment. No increase in polyamine biosynthesis was detected after topical skin treatment with 17 nanomole RA, but incorporation of [3H]thymidine increased at 42 hr. RA inhibited skin papillomas and carcinomas when administered with TPA treatments, but not when given with initiating doses of 7,12-dimethylbenz[a]anthracene (DMBA) after repeated TPA doses. RA did not promote growth of DMBA-induced tumors. Combined RA and DMBA treatment did not result in inhibition of induction of ODC or tumors. (58 Refs)

2. THE INFLUENCE OF TOPICAL AND ORAL RETINOID TREATMENT ON PHOTOCARCINOGENICITY IN HAIRLESS ALBINO MICE.

Hartmann HR, Teelman K
Pharma Forschung 2, F. Hoffman-La Roche and Co., AG, Grenzacherstrasse 124, CH-4002 Basel, Switzerland
Retinoids: Advances in Basic Research and Therapy, Proceedings of the International Dermatology Symposium held in Berlin, W. Germany, 13-15 October, 1980. Orfanos CE, Braun-Falco O, Farber EM, Grupper C, Polano MK, and Schuppli R, ed. Berlin, Springer-Verlag, 527 pp., 1981.

Female hairless albino mice (strain Fu-Alb hr/hr) were irradiated with simulated sunlight and treated either topically with a placebo, tretinoin (TT), or motretinid (MT), or po with a placebo or etretinate (ET). Topical or oral treatment was well-tolerated in all groups; no signs of local or systemic toxicity were observed. Few if any skin tumors (papillomas) developed in treated or untreated unirradiated mice. At the end of the topical treatment period, almost all irradiated animals carried multiple tumors on their backs. The mean tumor index of irradiated groups steadily increased during and after the treatment period. Local treatment with TT led to a marked increase in tumors in contrast to MT. Tumors were primarily of epithelial origin and were diagnosed as papillomas and focal or widespread squamous cell carcinomas. Most of the tumors seen were in a premalignant stage. Metastases of squamous cell carcinomas were observed on only two occasions. In unirradiated mice, only three animals develop one papilloma each. After termination of treatment, most irradiated mice carried multiple tumors on their backs. No significant difference was noted in the mean tumor indices of the three irradiation groups (placebo, 0.5 and 1.5 mg/kg ET) was noted. Histologically the skin of ET-treated unirradiated mice appeared to be free of any cutaneous effect. Skin alterations in the irradiated mice were macroscopically and microscopically similar to those in the topical treatment groups, except that a distinct shift to more focal or circumscribed carcinomas was evident in the ET-treated animals compared with all irradiated mice treated otherwise. The results indicated that neither topical MT nor po ET enhanced tumor formation while topical TT at doses one fiftieth and one fifth of clinical concentrations had a marked tumor enhancing effect. (16 Refs)

3. LACK OF ENHANCEMENT OF EXPERIMENTAL PHOTOCARCINOGENESIS BY RETINOIC ACID.

Kligman LH, Kligman AM
Dept. Dermatology, Univ. Hosp., Univ. Sch. Medicine, Philadelphia, PA, 19104
Retinoids: Advances in Basic Research and Therapy, Proceedings of the International Dermatology Symposium held in Berlin, W. Germany, 13-15 October, 1980. Orfanos CE, Braun-Falco O, Farber EM, Grupper C, Polano MK, and Schuppli R, ed. Berlin, Springer-Verlag, 527 pp., 1981.

The enhancement of photocarcinogenesis by retinoic acid (RA) was studied in lightly pigmented female SKh:hairless-2 mice. In mice treated with concomitant UV irradiation and topical RA applied to the abdominal skin, RA showed no effect on photocarcinogenesis with respect to tumor yield, latent period, or tumor progression. In mice treated with topical RA after tumor induction, a significantly higher rate of regression was noted in 0.001% RA-treated mice than in UV-treated controls. Biopsy of regressed lesions frequently revealed only remnants of the tumor. Compared to UV controls, tumorigenesis was inhibited following both the po and topical administration of RA. The mice pre-treated with RA had received enough of the drug to produce a mild lymphadenopathy indicating a systemic effect by both abdominal painting and po administration. In a two vehicle study in which RA was administered in polyethylene glycol with BHT or in methanol, there were no tumors in any of the groups after 58 wk, except for two 1 mm papillomas in the UV controls and three 1 mm papillomas in the UV-RA-methanol animals. The results indicated that no enhancement of photocarcinogenesis by RA was noted in lightly pigmented hairless mice as it appears to in albinos. (16 Refs)

4. DNA SYNTHESIS INHIBITORS (SKIN CHALONES AND HYDROXYUREA) ENHANCE TUMOUR PRODUCTION AFTER A SINGLE APPLICATION OF METHYLNITROSOUREA TO HAIRLESS MOUSE SKIN (MEETING ABSTRACT).

Iversen OH
McArdle Laboratory for Cancer Research, Madison, WI
Eighth European Congress of Pathology, August 30-September 4, 1981, Helsinki, Finland. The Congress 92 pp., 1981.

Hairless mouse epidermis was treated topically with 1 mg methylnitrosourea in acetone. Three groups had been given ip pretreatment with epidermal extracts, and one group with 5 mg hydroxyurea ip 30 min before the carcinogen. Control groups were injected with muscle- or skin extract, saline or Colcemid. One control group was without pretreatment. Contrary to expectations, the groups with depressed epidermal DNA synthesis by skin chalone or hydroxyurea developed significantly more tumors than the other groups. Hence, under the experimental conditions used, an inhibited DNA synthesis at the time of the carcinogen application significantly enhanced

carcinogenesis. Various possible mechanisms are discussed. (no Refs)

TUMOR PROMOTION AND COCARCINOGENESIS IN OTHER ANIMAL MODELS

5. EFFECT OF SOME FATTY ACID METHYL ESTERS ON GASTROINTESTINAL CARCINOGENESIS BY N-METHYL-N'-NITRO-N-NITROSOGUANIDINE IN RATS.

Arffmann EJ, Rasmussen KS, Hansen FN

Dept. Pathology, Aalborg Hosp., P.O. Box 561, DK-9100 Aalborg, Denmark

JNCI; 67(5):1071-1075 1981

Methyl linoleate hydroperoxide (MLHP) and native methyl linoleate (ML) were tested for carcinogenicity toward the gastrointestinal (GI) tract in male specific-pathogen-free outbred Wistar rats. N-Methyl-N'-nitro-N-nitrosoguanidine (MNNG) was given in the drinking water in a dose of 20 mg/liter when cocarcinogenic properties of the test substances were to be tested. MLHP and ML were fed by stomach tube and had no effect as complete carcinogens. Given concomitantly with MNNG, ML did not enhance carcinogenesis. MLHP in conjunction with MNNG was the only treatment which, as treatment with MNNG in a dose of 83 mg/liter, led to an increase of GI cancers in animals that died before day 354. Cumulative results after a max of 612 days showed a distribution of GI cancers in favor of the glandular stomach only after MLHP was given with MNNG. (Author abstract) (24 Refs)

6. ENHANCING EFFECT OF HYDROGEN PEROXIDE UPON DUODENAL AND UPPER JEJUNAL CARCINOGENESIS IN RATS.

Hirota N, Yokoyama T

Dept. Pathology, Jichi Medical Sch., Minamikawachi-machi Kawachi-gun, Tochigi-ken 329-04, Japan

Gan; 72(5):811-812 1981

A study of the incidence of intestinal carcinomas induced in rats by the oral administration of hydrogen peroxide (HP) and methylazoxymethanol acetate (MAMA) injections is reported. In Group A, 8/8 rats developed a total of 21 adenocarcinomas (AC) of the duodenum and 7 jejunal AC following oral administration of 1.5% HP for 21 wk with three ip injections of MAMA given at 2 wk interval during the HP administration. In Group B, 2/8 rats developed AC of the jejunum, and 1/8 developed colonic carcinoma following oral administration of HP for 8 wk including intervals between MAMA injections as in Group A. In Group B, however, HP drinking was discontinued following the injections. In Group C, hyperplastic epithelia of the duodenum and upper jejunum were observed in three rats on HP administration for 25 wk. No neoplastic changes were found in this group or in Group D of three untreated control rats. It is suggested that hyperplastic conditions preinduced by HP prior to the injection of MAMA may have contributed to the development of duodenal and upper jejunal AC. (2 Refs)

7. ENHANCING EFFECT OF BARBITAL ON N-2-FLUORENYLACETAMIDE-INDUCED RAT LIVER LESIONS.

Mori H, Tanaka T, Nishikawa A, Takahashi M, Williams GM

Dept. Pathology, Gifu Univ. Sch. of Medicine, 40 Tsukasa-machi, Gifu 500, Japan

Gan; 72(5):798-801 1981

The enhancing effects of phenobarbital (PB) and barbital on hepatotumorigenesis were compared by quantitative analysis of the behavior of altered foci following discontinuation of N-2-fluorenylacetamide (FAA) administration. Thirty-four male ACI rats, 2 mo old, were fed 0.02% FAA diet for 13 wk and some of them were sacrificed immediately. The remaining rats were divided into three groups and given a basal diet (Group I) or 0.05% PB diet (Group II) or 0.05% barbital diet (Group III) and sacrificed sequentially at 8 and 16 wk after the beginning of administration of each diet. The number of altered foci detected in hematoxylin and eosin stained or iron stained specimens per cm2 of the liver space at 16 wk in Group I was much lower than that at termination of FAA feeding. However, the numbers of Groups II and III were well maintained at 8 and 16 wk and those at 16 wk in both groups were significantly higher than that in Group I (p less than 0.001). These data show that barbital could be an enhancer of hepatotumorigenesis like PB. (Author abstract) (25 Refs)

8. INDUCTION OF GAMMA-GLUTAMYL TRANSPEPTIDASE POSITIVE FOCI IN RAT LIVER BY PYROLYSIS PRODUCTS OF AMINO ACIDS.

Tamano S, Tsuda H, Tatematsu M, Hasegawa R, Imaida K, Ito N

First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan

Gan; 72(5):747-753 1981

The activities of pyrolysis products for initiating or promoting preneoplastic lesions were tested. In experimental series I, N-2-fluorenylacetamide (2-FAA) was used as a initiator or a promoter and 3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole (Trp-P-1), 3-amino-1-methyl-5H-pyrido[4,3-b]indole (Trp-P-2), 2-amino-6-methyldipyrido[1,2-a:3',2'-d]imidazole (Glu-P-1) or 2-aminodipyrido[1,2-a:3',2'-d]imidazole (Glu-P-2) was administered at a fixed dose and for the same period in the initiation stage or the promotion stage. Animals were subjected to partial hepatectomy or treated with carbon tetrachloride (CCl4) to increase the induction of gamma-glutamyl transpeptidase (gamma-GT) positive foci. Trp-P-1 and Glu-P-2 administered in either the initiation or promotion stage significantly increased the induction of gamma-GT positive foci (p less than 0.001). Glu-P-1 increased the induction of gamma-GT positive foci (p l ess than 0.001) when administered in the initiation stage but it was not effective when administered during the promotion stage. In experimental series II, animals were given a single dose of these chemicals at one of the three different dose levels with partial hepatectomy and then were fed with 2-FAA and given a single dose of CCl4. Trp-P-1, Glu-P-1 and Glu-P-2 caused dose-dependent inductions of gamma-GT positive foci. (Author abstract) (14 Refs)

9. BLADDER CARCINOGENESIS IN MICE INDUCED BY N-BUTYL-N-(4-HYDROXYBUTYL)NITROSAMINE AND N-ETHYL-N-(4-HYDROXYBUTYL)NITROSAMINE WITH REFERENCE TO THE EFFECT OF CYCLOPHOSPHAMIDE.

Numoto S, Yoshida M, Otsuka H
Second Dept. Pathology, Sch. Medicine, Tokushima Univ., Kuramoto-cho 3-18-15, Tokushima 770, Japan
Gan; 72(5):647-654 1981

The carcinogenicities of N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) and N-ethyl-N-(4-hydroxybutyl)nitrosamine (EHBN) on the urinary bladder were compared in male BALB/c mice. The effect of cyclophosphamide (CPA) on the carcinogenicities was also investigated. The carcinogenic activity on the bladder mucosa of EHBN was similar to that of BBN, and there was no difference in the growth patterns, histological types or invasive characters of carcinoma induced by BBN and EHBN. Benign or malignant tumors of vascular origin developed in the urinary bladders of 15 mice treated with these carcinogens. The incidence of vascular tumors induced by EHBN was significantly higher than that of tumors induced by BBN. Ip injections of CPA seemed to have no effect in the incidence of bladder carcinomas induced by these carcinogens, or on the development of vascular tumors in the bladder wall induced by EHBN. (Author abstract) (18 Refs)

10. ENHANCEMENT BY RETINYL ACETATE OF HORMONE-INDUCED MAMMARY TUMORIGENESIS IN FEMALE GR/A MICE.

Welsch CW, Goodrich-Smith M, Brown CK, Crowe N
Dept. Anatomy, Michigan State Univ., East Lansing, MI, 48824
JNCI; 67(4):935-938 1981

Feeding of retinyl acetate (82 mg/kg ration) for 13-16 wk to estrone- and progesterone-treated nulliparous and multiparous inbred GR/A mice resulted in a substantial increase in the incidence of mammary carcinomas. Mammary carcinoma incidence in nulliparous control and retinoid-fed mice in experiment 1 was 22/65 (34%) and 37/65 (57%) (p less than 0.05), respectively; in experiment 2, 27/48 (56%) and 37/48 (77%) (p less than 0.05), respectively. Mammary carcinoma incidence in multiparous control and retinoid-fed mice in experiment 1 was 13/30 (43%) and 23/30 (77%) (p less than 0.05), respectively; in experiment 2, 19/19 (100%) and 19/19 (100%), respectively. The purported chemopreventive activities of retinyl acetate in murine mammary tumorigenesis were not demonstrated in this study; indeed, the vitamin A analog appeared to enhance this oncogenic process in the steroid hormone-treated GR mouse mammary cancer model. (Author abstract) (25 Refs)

IN VITRO STUDIES OF TUMOR PROMOTERS

11. DIFFERENTIAL RESPONSE OF PREMALIGNANT EPITHELIAL CELL CLASSES TO PHORBOL ESTER TUMOR PROMOTERS AND TO DEOXYCHOLIC ACID.

Friedman EA
Dept. Gastrointestinal Cancer Res., Div. Molecular Biology and Genetics, Graduate Sch., Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Cancer Res; 41(11,part1):4588-4599 1981

The effects of two agents, 12-O-tetradecanoylphorbol-13-acetate (TPA) and deoxycholic acid (DOC), which act as tumor promoters in the gastrointestinal epithelium of experimental animals, were compared using primary cultures of human premalignant colonic epithelial cells at different stages in tumor progression. Both DOC and TPA enhanced the size of the proliferative fraction in colonies of early-stage premalignant cells, with DOC providing more stimulation. TPA-treated intermediate- and late-stage premalignant cells elongated and then disrupted the monolayer by forming rills several cells in thickness and then multicellular clusters. This multilayering was reminiscent of the areas of carcinoma found within adenomas. DOC had no such effects on morphology. Cell clustering was concomitant with secretion of a protease with characteristics of a plasminogen activator. Premalignant cells secreted severalfold higher levels of protease in response to TPA than did either TPA-treated primary cultures of colonic adenocarcinomas or established colon carcinoma cell lines. These results suggest that (a) DOC and TPA act sequentially during tumor promotion and (b) cell clustering and protease release may be associated with the transition of premalignant epithelial cells to colonic carcinoma. (Author abstract) (43 Refs)

12. SPECIFIC BINDING OF TRANSFORMING GROWTH FACTOR CORRELATES WITH PROMOTION OF ANCHORAGE INDEPENDENCE IN EGF RECEPTORLESS MOUSE JB6 CELLS.

Colburn NH, Gindhart TD
Lab. Viral Carcinogenesis, NCI, Frederick, MD, 21701
Biochem Biophys Res Commun; 102(2):799-807 1981

Promotion of anchorage independence by a transforming growth factor is reported. JB6 mouse epidermal cells were exposed in vitro to 12-O-tetradecanoyl-phorbol-13-acetate (TPA: 1.6 x 10(-8) M), epidermal growth factor (EGF: 2 or 20 nanog/ml), or transforming growth factor (TGF: 5 ug/ml) derived from a human rhabdomyosarcoma line. Binding was measured using 125I-labeled EGF and TGF. Some clones of JB6 cells, such as clone 41, were sensitive to both EGF and TPA, while others were resistant to both. Sensitivity was measured by colony formation in 0.33% agar. Most of the colonies produced by TPA, EGF, or TGF gave rise to transformed cell lines which formed colonies in agar without inducer. A TPA-resistant derivative cell line of clone 41, R219, did not bind EGF specifically. Anchorage independence could be induced in R219 b y TPA or TGF, but not by EGF. These cells appeared to have a class of binding sites specific for TGF in addition to sites binding EGF. The EGF sites, which also bind TGF, evidently were not necessary for transformation by TGF. (16 Refs)

13. RELATIONSHIP OF INCREASED GROWTH CAPACITY AND TUMOR PROMOTION IN CULTURED RAT TRACHEAL EPITHELIAL CELLS (MEETING ABSTRACT).

Steele VE, Beeman DK
National Institute of Environmental Health Sciences, Box 12233, Research Triangle Park, NC, 27709
In Vitro; 17(3):202 1981

Previously carcinogens and more recently the tumor promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA) have been shown to increase the growth capacity of cultured tracheal epithelial cells. Our aim was to relate this heritable growth alteration with the ability of various compounds to promote chemical carcinogenesis. Rat tracheal organ cultures were exposed on Days 9, 15, 21, and 27 of culture to the promoting/nonpromoting substances in serum-free medium for 1 hr. The

exposure concentrations were 1 ug/ml in 0.2% dimethylsulfoxide. Primary epithelial cell cultures were established from explant outgrowth cultures and alterations in growth capacity were measured by the ability to establish a cell line. We were able to establish a high percentage of cell lines from TPA and benzo(a)pyrene exposed explants. No cell lines were derived from mezerine, acetic acid or benzo(e)pyrene exposed explants. Phorbol and 4-O-methyl-12-O-tetradecanoylphorhol-13-acetate exposures led to the establishment of a low percentage of cell lines. It was also found that epithelial cell lines can also be established from monolayer primary cell cultures exposed to TPA with a high efficiency. The growth response of cultured tracheal epithelial cells to various tumor promoters/nonpromoters appears to correlate well with the in vivo properties of these compounds as demonstrated in mouse skin. (no Refs)

14. EFFECT OF THE TUMOR PROMOTER PHENOBARBITAL ON MEMBRANE-MEDIATED PROPERTIES OF ADULT RAT LIVER-DERIVED EPITHELIAL CELLS IN CULTURE (MEETING ABSTRACT).

Shimada T, Kreiser DM, Williams GM
Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, NY, 10595
In Vitro; 17(3):224 1981

We have reported a promoting action of phenobarbital on the transformation of adult rat liver (ARL) epithelial cells in culture. We report here various other biological effects of phenobarbital (PB) which mimic induction of transformation on ARL cells. A clonal line of ARL cells, which was proved to be nontumorigenic when examined for transformation markers, was seeded at a density of 1.2 x 10(4) cells/cm2 in Williams Medium E supplemented with heat-inactivated fetal bovine serum at 10% (WME:HIFBS(10)) with gentamicin at 50 ug/ml. Cells were fed with WME:HIFBS10 containing 10(-4) M PB 2 x a wk starting 24 hr after seeding and subcultured once a wk at the same seeding density. Cells that received multiple treatments of PB showed a 10-20% increase in cell population at each subculture up to 10 treatments, and continued to increase in 2-Deoxy-D-glucose (2DG) uptake in the absence of PB by as much as 77% after 22 treatments. On the other hand, single PB treatment of ARL cells did not enhance 2DG uptake. Neither single nor multiple treatments with PB induced anchorage independency in ARL cells. It is suggested that the alteration of plasma membrane properties by PB, as in vivo could be the mechanism of the tumor promoting activity of PB. (2 Refs)

15. MAINTENANCE BY SACCHARIN OF MEMBRANE ALTERATIONS OF RAT BLADDER CELLS INDUCED BY SUBCARCINOGENIC TREATMENT WITH BLADDER CARCINOGENS.

Kakizoe T, Komatsu H, Niijima T, Kawachi T, Sugimura T
Urology Div., Natl. Cancer Center Hosp., Tsukiji 5-1-1, Chuo-ku, Tokyo 104, Japan
Cancer Res; 41(11,part1):4702-4705 1981

Saccharin is known to have a tumor-promoting effect on bladder cancer in rats, but its mechanism of action is unknown. We demonstrated that the increased agglutinability of isolated epithelial cells of the bladder in the presence of concanavalin A caused by a subcarcinogenic dose of bladder carcinogens disappeared shortly after the end of their administration. However, saccharin maintained the increased agglutinability when given continuously after administration of carcinogen. Moreover, the agglutinability of bladder cells previously exposed to a subcarcinogenic dose of bladder carcinogens increased again when saccharin was given after the agglutinability had disappeared completely. (Author abstract) (23 Refs)

16. INHIBITION OF MYOGENESIS IN HUMAN MUSCLE CULTURES BY PHORBOL ESTER TUMOR PROMOTERS (MEETING ABSTRACT).

Miranda AF, Fisher PB, Weinstein IB
Columbia University College of Physicians and Surgeons, New York, NY, 10032
In Vitro; 17(3):202 1981

Tumor promoters are potent inhibitors or inducers of cell differentiation, depending on the specific target cells. Improved techniques now make it possible to analyze myogenesis in regenerating human skeletal muscle cultures from both normal and diseased tissued. We evaluated the effect of phorbol ester tumor promoters on myogenesis in normal human muscle. The degree of differentiation was determined by the fraction of total cell nuclei in multinucleated myotubes formed in monolayer cultures of single clones, and the conversion of embryonic creatine kinase (BB) to the mature skeletal muscle form (MM). The potent tumor promoter 12-O-tetradecanoyl-phorbol-13-acetate (TPA), but not its inactive analog phorbol, induced a dose-dependent inhibition of myotube formation and creatine kinase isoenzyme transition. This was not associated with toxicity. All treated cultures eventually escaped from the TPA inhibitory effect and differentiated. Addition of Ca++ to Ca++-depleted cultures normally results in rapid fusions. Simultaneous addition of TPA and Ca++ to Ca++-depleted cultures inhibited fusion, suggesting a direct effect of TPA on membrane fusion events. The results provide the first example in which TPA inhibits differentiation of a human cell culture system, and should prove valuable in analyzing the complex process of carcinogenesis. (no Refs)

17. GENERATION OF 1,2-DIACYLGLYCEROL IN PLASMA MEMBRANES OF PHORBOL ESTER-TREATED MYOBLASTS.

Grove RI, Schimmel SD
NIEHS, Room 418, Building 4, NIH P. O. Box 12233, Research Triangle Park, NC, 27709
Biochem Biophys Res Commun; 102(1):158-164 1981

The effect of tumor promoter 12-O-tetradecanoylphorbol 13-acetate (TPA) on lipid metabolism was studied in a culture of chick embryo differentiated myoblasts. TPA (20 nanog/ml) caused a 2x increase in 1,2-diacylglycerol (DAG) levels within 30 min. Weakly or non-promoting TPA analogs 12-O-decanoylphorbol 13-acetate and 4-alpha-phorbol 12,13 didecanoate had little or no effect. DAG was shown to be generated from pre-existing lipids rather than from de novo synthesis. (26 Refs)

18. BIOCHEMICAL BASIS OF ACTION OF PHORBOL ESTERS ON PANCREATIC ACINAR CELLS: A NEW MECHANISM FOR STIMULATING SECRETION (MEETING ABSTRACT).

Jensen RT, Lemp GF, Gardner JD
National Institutes of Health, Bethesda, MD, 20205
Gastroenterology; 80(5,part2):1184 1981

TPA (12-O-tetradecanoyl-phorbol-13-acetate) is a potent tumor-promoting agent extracted from croton oil. In the present studies we examined the biochemical basis of action of TPA on dispersed acini from guinea pig pancreas. TPA caused a 20-fold increase in amylase secretion and was 70 percent

more efficacious than a maximally effective concentration of cholecystokinin (CCK). Detectable stimulation of amylase secretion occurred with 3nM TPA, half-maximal stimulation with 0.1 uM and maximal with 30uM. The action of TPA on enzyme secretion was not altered by secretagogues that cause mobilization of cellular calcium (CCK, carbachol, bombesin, A23187) but was potentiated by secretagogues that increase cellular cyclic AMP (vasoactive intestinal peptide, secretin). TPA, however, did stimulate calcium uptake by pancreatic acini and the dose-response curve for stimulation of calcium uptake was the same as that for stimulation of enzyme secretion. These results indicate that the actions, of TPA on pancreatic acini are unique in two respects: 1) TPA is the most effective pancreatic secretagogue examined to date; 2) although the action of TPA is calcium-mediated, TPA acts by increasing the inward movement of calcium into acinar cells, not by causing mobilization of intracellular calcium. Furthermore, the close correlation between the relative abilities of phorbol esters to stimulate pancreatic enzyme secretion and the abilities of the se agents to promote carcinogenesis suggests that these two effects may be caused by a common calcium-mediated mechanism. (no Refs)

19. PROTEASE INHIBITOR ANTIPAIN SUPPRESSES 12-O-TETRADECANOYL-PHORBOL-13-ACETATE INDUCTION OF PLASMINOGEN ACTIVATOR IN TRANSFORMABLE MOUSE EMBRYO FIBROBLASTS.

Long SD, Quigley JP, Troll W, Kennedy AR
Lab. Radiobiology, Harvard Univ. Sch. Public Health, 665 Huntington Ave., Boston, MA, 02115
Carcinogenesis; 2(9):933-936 1981

Normal and transformed mouse 10T1/2 fibroblasts were treated with the tumor promoter 12-O-tetradecanoyl-phorbol-13-acetate (TPA) and with several protease inhibitors. TPA induced cell-associated plasminogen activator (PA) activity in normal fibroblasts, and did not affect the PA activity already present in transformed fibroblasts. Antipain inhibited PA activity in both normal and transformed 10T1/2 cells. The protease inhibitors leupeptin and soybean trypsin inhibitor failed to affect PA activity in either cell line. (28 Refs)

20. TUMOR PROMOTERS ALTER GENE EXPRESSION AND PROTEIN PHOSPHORYLATION IN AVIAN CELLS IN CULTURE.

Laszlo A, Radke K, Chin S, Bissell MJ
Lab. Cell Biology, Div. Biology and Medicine, Univ. California, Berkeley, CA, 94720
Proc Natl Acad Sci USA; 78(10):6241-6245 1981

We have investigated the effect of 12-O-tetradecanoylphorbol 13-acetate (TPA) on the synthesis and modification of polypeptides in normal avian cells and cells infected by wild-type and temperature-sensitive Rous sarcoma virus (RSV). Using two-dimensional gel electrophoresis, we have detected alterations in both the abundance of cellular polypeptides and in their phosphorylation that seem unique to TPA treatment. However, the state of phosphorylation of the major putative substrate for the action of the src gene-associated protein kinase, the 34-to 36-kilodalton protein, was not altered. Moreover, examination of the phosphorylated amino acid content of total cellular phosphoproteins revealed that the response to TPA was not associated with detectable increases in their phosphotyrosine content. These results make it unlikely that TPA acts by the activation of the phosphorylating activity of the cellular proto-src gene or by the activation of other cellular phosphotyrosine-specific kinases. We have shown previously that temperature-sensitive RSV-infected cells at nonpermissive temperature demonstrate an increased sensitivity to TPA treatment. Our present results indicate that this is not due to reactivation of the phosphorylating activity of the defective src gene product or to its leakiness, and they lend support to the notion of multistep viral carcinogenesis. (Author abstract) (29 Refs)

21. TUMOR-PROMOTING PHORBOL DIESTER-INDUCED SPECIFIC CHANGES IN CELL SURFACE GLYCOPROTEIN PROFILE OF K562 HUMAN LEUKEMIC CELLS.

Fukuda M
Biochemical Oncology, Fred Hutchinson Cancer Res. Center, Seattle, WA, 98104
Cancer Res; 41(11,part1):4621-4628 1981

The tumor-promoting phorbol ester, 12-O-tetradecanoylphorbol-13-acetate (TPA), induced specific changes in the cell surface glycoprotein profile of K562 human leukemic cells. TPA-treated K562 cells were examined by cell surface labeling followed by immunoprecipitation with anti-glycophorin antiserum or anti-K562 antiserum. TPA-treated K562 cells lost glycophorin and glycoprotein with a mol wt of 105,000, which are specific to later stages of erythroid cell differentiation, and retained glycoprotein with a mol wt of 95,000, which is specific to early stages of erythroid cell differentiation. On the other hand, 4alpha-phorbol-12,13-didecanoate, which is inactive as a tumor promoter, induced no significant changes in cell surface glycoproteins of K562 cells. In parallel, TPA induced morphological changes of K562 cells as their growth was inhibited, whereas 4alpha-phorbol-12,13-didecanoate had no effect on these two characteristics. Thus, the tumor promoter induced specific changes in the cell surface glycoprotein profile of K562 human leukemic cells, which appeared to be induced into a retrodifferentiated stage. (Author abstract) (51 Refs)

22. STEROIDS INHIBIT TUMOR PROMOTING AGENT INDUCED EPSTEIN-BARR VIRUS EARLY ANTIGENS IN RAJI CELLS.

Sundar SK, Ablashi DV, Armstrong GR, Zipkin M, Faggioni A, Levine PH
Div. Cancer Cause and Prevention, NCI, Bethesda, MD, 20205
Int J Cancer; 28(4):503-507 1981

Four steroids and one protease inhibitor were evaluated for their effects on 12-O-tetradecanoyl phorbol 13-acetate (TPA)-induced and Epstein-Barr virus-induced early antigens (EBV-EA) in Raji cells. Continuous treatment with dexamethasone, prednisolone, hydrocortisone and cortisone inhibited TPA-induced EBV-EA to varying degrees, but the protease inhibitor N-alpha-p-tosyl L-lysine chloromethyl ketone-HCl (TLCK) had no significant effect. None of the agents tested inhibited EBV-induced EA. In addition, the effect of the steroids was reversible since the removal of these agents resulted in recovery of the percentage of EBV-EA-positive cells in TPA-treated cultures. These results were in agreement with the in vivo experiments of other investigators, who demonstrated inhibition of tumor promotion with steroids. Since TLCK failed to inhibit TPA-induced EA, it is unlikely that induction of EA by TPA is the result of production of proteases. (Author abstract) (36 Refs)

ANTICARCINOGENESIS BY CHEMICAL AGENTS

23. CHEMOPREVENTION OF MAMMARY TUMORIGENESIS BY A COMBINED REGIMEN OF SELENIUM AND VITAMIN A.

Ip C, Ip MM
Dept. Breast Surgery, Roswell Park Memorial Inst., Buffalo, NY, 14263
Carcinogenesis; 2(9):915-918 1981

The effect of combined administration of selenium (Se) and retinyl acetate (RA) was studied in female Sprague-Dawley rats with 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary gland tumors. DMBA was given intragastrically at 5 mg/wk for 3 wk. Starting 2 wk before initiation of DMBA administration, rats were fed a diet supplemented by Se (4 mg/kg) and/or RA (250 mg/kg) for 26 wk. Incidence of mammary gland tumors in rats exposed to DMBA alone was 90.0%, compared with 53.3% in rats treated with Se alone, 46.7% in rats treated with RA alone, 16.6% in rats treated with Se + RA for 28 wk, and 50.0% in rats treated with Se + RA-supplemented diet for only 18 wk. (32 Refs)

24. BIOCHEMICAL AND CLINICAL EFFECTS OF SELENIUM ON DIMETHYLHYDRAZINE-INDUCED COLON CANCER IN RATS.

Jacobs MM, Forst CF, Beams FA
Eppley Inst. Res. Cancer, Univ. Nebraska Medical Center, Omaha, NE, 68105
Cancer Res; 41(11,part1):4458-4465 1981

The biochemical and clinical effects of selenium (Na2SeO3) on 1,2-dimethylhydrazine (DMH)-induced colon carcinogenesis in male Sprague-Dawley rats are presented. A 4-ppm selenium supplement to the drinking water was provided before, during, and after 20 weekly injections of 20 mg DMH per kg body wt. Immediately after the 20th DMH injection, part of the rats were sacrificed. The incidences of colon tumors in groups provided selenium before DMH, before and during DMH, and only during DMH treatment were reduced to 39, 43, and 36%, respectively. The incidence in the DMH only control was 63%. Other rats in all treated and control groups were maintained up to 5 mo post-DMH treatment. At 10-wk intervals throughout the study, selected blood and tissue components were analyzed. The following hematological changes correlated with DMH treatment. (a) Serum glutamic oxalacetic transaminase increased 2-fold (normal, 66 +-14 g/dl). (b) Serum alkaline phosphatase increased 24% (normal, 166 +-56 units/liter). (c) Serum protein decreased 14% (normal, 6.77 +-0.48 g/dl). (d) White blood count increased 2-to 3-fold (normal, 7.7 +-2.7 x 10(3)/cu mm). And (e) Hb decreased 67% (normal, 18.1 +-1.3 g/dl). The magnitude of these changes varies with each selenium treatment group and with each 10-wk analysis period. Provision of 4 ppm selenium doubled both liver and blood selenium levels compared to supplemented controls. The effects of selenium and DMH treatments on glutathione peroxidase and beta-glucuronidase activities and on sialic acid are presented. Possible mechanisms by which selenium protect against DMH-induced neoplasia are discussed. (Author abstract) (40 Refs)

25. THE INFLUENCE OF SODIUM SELENITE ON TUMOR INDUCTION BY METHYLNITROSOUREA (MNU) IN RATS.

Warzok R, Thust R, Mendel J, Herbst C, Eismann C
Inst. Pathology, Ernst Moritz Arndt Univ., Friedrich-Loeffler-Str. 23e, DDR-2200 Greifswald, E. Germany
Arch Geschwulstforsch; 51(6):503-508 1981

The effect of sodium selenite (SS) on tumor induction by methylnitrosourea (MNU)was studied. Three groups of inbred strain WE rats (40 rats/group) were treated. Group I received MNU (20 mg/kg body wt/injection ip) in 20 injections at 4-wk intervals and 4 ppm SS in drinking water for 10 mo beginning with the first injection. Group II received only MNU treatment. Group III received only SS treatment. All animals in Groups I and II died by day 330, when Group III animals were killed. Rats not surviving 100 days were excluded from study. A total of 129 tumors in various sites developed in 39 rats in Group I. Group II showed 108 tumors in 35 rats. The difference between Groups I and II was not significant. No tumors developed in Group III rats. SS did not appear to affect MNU tumor induction. (27 Refs)

26. EFFECT OF INDOMETHACIN ON INTESTINAL TUMORS INDUCED IN RATS BY THE ACETATE DERIVATIVE OF DIMETHYLNITROSAMINE.

Pollard M, Luckert PH
Lobund Lab., Univ. Notre Dame, Notre Dame, IN, 46556
Science; 214(4520):558-559 1981

Over the course of 20 wk, Sprague-Dawley rats developed intestinal tumors in response to an ip injection of the acetate derivative of dimethylnitrosamine. The same agent did not induce tumors in Lobund-Wistar rats. The number of tumors was significantly smaller in rats given drinking water containing indomethacin (beginning 14 days after the injections) than in control rats given drug-free water. (Author abstract) (12 Refs)

MODIFICATION BY DIETARY FACTORS

27. FAILURE OF DIETARY CELLULOSE FIBER TO PREVENT COLON TUMORS IN DIMETHYLHYDRAZINE (DMH)-TREATED RATS ON HIGH CHOLESTEROL DIETS (MEETING ABSTRACT).

Tempero MA, West W, Zetterman RK
Department of Internal Medicine, Veterans Administration Medical Center, Omaha, NE, 68105
Gastroenterology; 80(5,part2):1301 1981

A prior study has suggested that dietary fiber (cellulose) may decrease colon carcinogenesis in the DMH-induced rat model. We have evaluated the effect of dietary cellulose fiber on DMH-induced colon tumors in rats fed high cholesterol diets (a suspected co-carcinogen with DMH). Synthetic diets containing excess cholesterol and variable fiber content were fed to male Sprague-Dawley rats: Group I (0% fiber), Group II (5% fiber), and Group III (20% fiber). Half of each group received sc injections of DMH for 20 wk. Control rats received saline. All animals were sacrificed 1 wk after the last injection and blood obtained for cholesterol determination. Rat colons were inspected grossly and microscopically for invasive adenocarcinoma. Saline control animals were tumor free. No

difference in either tumor incidence or number of tumors per affected rat colon was observed. Furthermore, the presence of dietary fiber did not alter serum cholesterol level supporting prior observations that cellulose fiber does not affect cholesterol m etabolism. These findings suggest excess dietary cholesterol may diminish the protective effect of dietary fiber on DMH-induced colon tumors, possibly through an intraluminal mechanism. (1 Ref)

MODIFICATION BY HORMONAL FACTORS

28. THE ROLE OF THYROID HORMONE IN RADIATION AND CHEMICALLY INDUCED ONCOGENESIS (MEETING ABSTRACT).

Borek C, Guerrsey DL, Ong A
Department of Radiology, Columbia University, College of Physicians and Surgeons, New York, NY, 10032
In Vitro; 17(3):203 1981

Neoplastic transformation in vitro by x-rays and chemical carcinogens has established the direct oncogenic potential of radiation and chemicals in mammalian cells. Little is known whether hormones, normally present in mammalian serum, can affect this response. Using short-term cultures of diploid hamster embryo cells, and the heteroploid mouse cell line C3H 10T1/2 we studied the effect of triiodothyronine (T3) on transformation. We have found that in both cell types the removal of thyroid hormone from serum-supplemented culture medium (using AG1-X10 resin) inhibits radiation and chemically induced transformation while having no effect on cellular growth rate or survival. When T3 alone is added to thyroid-depleted medium at 10(-7) M, transformation frequency induced by radiation is expressed at a similar frequency as in the presence of culture medium supplemented with untreated serum. We find that exposing the cells to T3 ranging from 10(-11) M to 10(-7) M results in radiation transformation which is dose dependent. Thyroid hormone is essential for the induction and/or expression of x-ray-induced transformations. Recent findings using Benzo-a-pyrene instead of x-rays as the oncogenic agent, indicate that in the absence of T3 there is no transformation and that T3 is required for the induction and/or expression of neoplastic transformation by the chemical carcinogen. (no Refs)

29. THE MULTIPLE ROLES OF ESTROGEN IN ESTROGEN-DEPENDENT RENAL CLEAR-CELL CARCINOMA OF SYRIAN HAMSTER (MEETING ABSTRACT).

Liehr JG, DaGue BB, Ballatore AM, Sirbasku DA
Department of Biochemistry and Molecular Biology, University of Texas Medical School, Houston, TX, 77025
Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

Estrogen (estradiol [E2] or diethylstilbestrol [DES]), when implanted subcutaneously into male Syrian hamster, elicits renal clear-cell carcinoma after approx 6-8 mo. Estrogen alone causes this effect, ie no cocarcinogen is required for tumor initiation or growth response. Studies conducted in our laboratories and elsewhere indicate that the elevated level of estrogen in the hamster results in a variety of different responses and biochemical effects which in a concerted fashion lead to the pheno menon called renal clear-cell carcinoma. Tumor initiation by Estrogen: DES and E2 induce peroxidase activity and microsomal P450 enzymes in a variety of tissues. In turn, peroxidase and microsomal P450 enzymes oxidize DES to a quinoid structure. DES quinone, a chemically unstable and reactive substance, may spontaneously rearrange to beta-dienestrol or, in the vicinity of cellular macromolecules, may covalently bind to DNA. DES-DNA adduct formation was studied in vitro under various conditions. Estrogen Dependence of Tumor Growth: H301 tumor cells, which are derived from the estrogen-dependent renal clear-cell carcinoma of Syrian hamster, remain estrogen-dependent in culture or in host animals. Upon removal of the hormone implant, tumors immediately shrink in size and disappear within 10 days. Estrogen concentration in tumor tissue is low (12-30% of estrogen uptake of liver), despite the presence of estrogen receptors in tumor tissue. (no Refs)

30. PRODUCTION OF OVARIAN TUMORS BY HORMONE ADMINISTRATION.

Araki S
Dept. Obstetrics and Gynecology, Kurume Univ. Sch. Medicine, Kurume 830, Japan
Kurume Med J; 28(1):35-43 1981

The influence of hormone administration on tumor production was studied in female Wistar rats implanted with chemical carcinogens (9,10-dimethyl-1,2-benzathracene (DMBA), 20-methylcholanthrene, (MC), 3,4-benzpyrene (BP), or 4-nitroquinolin-N-oxide (NQO)). The hormones were an estriol preparation (EST), a progesterone preparation (PROG), a testosterone preparation (AND), a dexamethasone preparation (ACH), and human chorionic gonadotropin (HCG). The incidence of solid tumors was highest with DMBA, less with MC and lowest with BP and NQO. ACH and EST appeared to accelerate tumor growth: the incidence of solid tumors at 20 wk was not significantly different, while at 40 wk it increased to 90% in the ACH group. Up to 20 wk in the hormone-treated groups, tumor incidence was low; however, the tumor incidence increased thereafter. The highest total incidence of cystic tumor was found in the EST group, compared to controls. The solid tumors included fibromas, sarcomas, and adenocarcinomas. In the AND, PROG, and EST groups, the tumors were either fibroadenomas or fibromas. In the HCG group fibroadenomas predominated. Sarcomas appeared in the 30th and 40th wk in the controls and the EST and PROG groups, respectively. The av wt of the tumors produced by ACH and EST was greater than the control, with the largest tumor in the EST group. (27 Refs)

31. THE BINDING OF 7,12-DIMETHYLBENZ[A]ANTHRACENE TO MAMMARY GLAND MACROMOLECULES IN THE HAMSTER: EFFECTS OF ENOVID FEEDING OR TRANSPLACENTAL EXPOSURE TO DIETHYLSTILBOESTROL.

Hertzog PJ, Lawson TA, Gingell R
Cancer Res. Unit, Univ. York, Heslington, York YO1 5DD, England
Chem Biol Interact; 37(1):199-205 1981

The covalent binding of 7,12-[3H]dimethylbenz[a]anthracene ([3H]DMBA) to mammary gland macromolecules was studied in hamsters fed a contraceptive mixture, Enovid, those exposed transplacentally to diethylstilbestrol (DES), and controls. Compared with rats, hamsters are relatively resistant to DMBA mammary carcinogenesis, but susceptibility is increased by either of the above treatments with Enovid or DES. The amount of DMBA bound to DNA and protein was 4-5x greater than to RNA, but only DNA binding was persistent. Fifty-

three percent of the DNA-bound DMBA was still present after 8 days. The amount of DMBA bound to hamster mammary DNA and its persistence was similar to that found in rats. Neither Enovid nor DES treatment altered the levels of binding to mammary macromolecules, nor their persistence. These results indicate that the species differences in the susceptibility to DMBA-induced mammary carcinogenesis in hamsters and rats, and modification of the former by hormones, is not due to differences in the activation of carcinogens. The role of hormones such as prolactin in the promotion phase of mammary gland carcinogenesis may explain these differences. (Author abstract) (18 Refs)

32. REVERSIBLE INHIBITION OF RAT HEPATOCYTE PROLIFERATION BY HYDROCORTISONE AND ITS EFFECT ON CELL CYCLE-DEPENDENT HEPATOCARCINOGENESIS BY N-METHYL-N-NITROSOUREA.

Kaufmann WK, Kaufman DG, Rice JM, Wenk ML
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Cancer Res; 41(11,part1):4653-4660 1981

The susceptibility of hepatocytes to carcinogenesis in vivo may be influenced by the phase of the cell cycle at which carcinogen-induced damage is incurred. In order to better understand this relationship, hepatic cell proliferation in juvenile male Fischer 344 rats was charted following a two-thirds partial hepatectomy. For hepatocytes, two distinct waves of DNA synthesis occurred which were followed after 6 to 8 hr by waves of mitotic cell division. In contrast to this kinetic pattern, when hydrocortisone was given after the partial hepatectomy, the initial waves of DNA synthesis and mitosis by hepatocytes were each delayed by about 15 hr. In rats not given hydrocortisone, susceptibility to hepatocarcinogenesis by N-methyl-N-nitrosourea was greatest at 20 hr after partial hepatectomy when the peak fraction of proliferating hepatocytes was in the S phase. By shifting the time of onset of DNA synthesis, the hydrocortisone treatments also shifted the time with greatest sensitivity to N-methyl-N-nitrosourea, with hepatocytes in late G1 or S again the most susceptible. Numerous tumors were also induced by N-methyl-N-nitrosourea in extrahepatic tissues, including intestine, Zymbal's gland, nervous system, kidney, odontogenic tissues, and peritesticular mesothelium. The results illustrate the importance of cell proliferation in carcinogenesis and further point to the specific sensitivity of certain cell cycle phases. (Author abstract) (31 Refs)

MODIFICATION BY VIRUSES, IMMUNE FACTORS OR IRRADIATION

33. CHEMICAL-VIRAL CO-CARCINOGENESIS IN VITRO USING CLONED MAMMARY EPITHELIAL CELLS AND MOUSE MAMMARY TUMOR VIRUS (MEETING ABSTRACT).

Howard DK, Fisher PB, Schlom J
National Cancer Institute, National Institutes of Health, Bethesda, MD, 20205
In Vitro; 17(3):236 1981

We have evaluated the effect of mouse mammary tumor virus (MMTV) and 7,12-dimethylbenz(a)anthracene (DMBA), either alone or in combination, on mammary epithelial cells in vitro. A single-cell clone (clone 2), was derived from the normal mouse mammary gland cell line, C57MG, and was shown to be of murine origin by karyotyping, isoenzyme analyses, and by immunofluorescence using species-specific antisera. This clone failed to induce tumors in syngeneic or athymic (nude) mice. The epithelial origin of the cells was demonstrated by the presence of desmosomes, tonofibrils and secretory granules. Clone 2 cells were infected with MMTV host-range variant MMTV (RIII) vp4, and both infected and mock-infected cultures were treated with DMBA. Cultures treated with both virus and carcinogen exhibited morphological changes and a slight increase in ability to grow in soft agar after 5 to 7 subcultures. The most striking alteration in the phenotype of cells exposed to the combination of MMTV and DMBA, however, was an increase in their tumorigenic potential in athymic mice. Cultures treated with virus alone or DMBA alone did not show an increase in tumorigenicity. This cell-culture model system now permits the study of the interaction of chemicals and MMTV in the initiation and promotion of mammary cell transformation. (no Refs)

34. DEMONSTRATION OF A SYNCARCINOGENIC EFFECT OF ENDOGENOUS MULV, RESCUED FROM MNU-INDUCED LEUKEMIAS, AND SUBOPTIMAL MNU DOSES IN MICE.

Fey F, Ehm I, Drescher B, Rentz E, Seidel G
Acad. Sciences of GDR, Central Inst. Cancer Res., 1115 Berlin, E. Germany
Neoplasma; 28(3):265-269 1981

It was demonstrated that the combined action of activated endogenous MuLV isolated from MNU-induced leukemias and suboptimal doses of MNU yields a significantly high incidence of leukemias and tumors. Treatment with one agent alone shows low effects only. The findings were discussed in view of the mechanisms in which viruses and chemical carcinogens interact in a syncarcinogenic process. (Author abstract) (11 Refs)

OTHER RELATED STUDIES

35. COMPARATIVE STUDIES ON THE PRODUCTION OF STOMACH TUMORS FOLLOWING THE INTUBATION OF SEVERAL DOSES OF N-METHYL-N'-NITRO-N-NITROSOGUANIDINE IN GERM-FREE AND CONVENTIONAL NEWBORN RATS.

Sumi Y, Miyakawa M
Lab. Germfree Life Res., Nagoya Univ. Sch. Medicine, 65 Tsuruamicho, Showa-ku, Nagoya 466, Japan
Gan; 72(5):700-704 1981

The present work was undertaken to investigate the possible role of microflora in gastric tumorigenesis by the comparison of tumor production between germ-free and conventional male Wistar rats given the same amount of N-methyl-N'-nitro-N-nitrosoguanidine into the stomach by catheter during the newborn period. Only 29% of germ-free rats treated with 450 ug/animal that were killed 300 days after the first intubation had tumors in the stomach, whereas 93% of conventional similarly treated rats had such tumors at the same period, suggesting that the microflora might exert a promoting influence upon stomach tumor production. (Author abstract) (27 Refs)

36. EFFECT OF ANTIBIOTICS ON INCIDENCE OF RAT INTESTINAL TUMORS INDUCED BY 1,2-DIMETHYLHYDRAZINE DIHYDROCHLORIDE.

Goldin BR, Gorbach SL

Infectious Disease Service, Dept. Medicine, New England Medical Center Hosp., Tufts Univ. Sch. Medicine, 171 Harrison Ave., Boston, MA, 02111

JNCI; 67(4):877-880 1981

The intestinal microflora has been shown to influence the induction of chemical carcinogens responsible for intestinal tumors in animal models. For further exploration of this issue, male inbred F344 rats were administered a chemical carcinogen, 1,2-dimethylhydrazine dihydrochloride (DMH), for 20 wk, along with oral antibiotics, either tetracycline or erythromycin, to suppress the intestinal flora. Colon cancer incidence was lower in animals receiving antibiotics; 22% of the erythromycin-treated rats and 20% of the tetracycline-treated rats had colon tumors compared to untreated controls with a 74% tumor incidence (p less than 0.002). Tumors in the small intestine also decreased from an incidence of 48% in the control animals to an incidence of 27 and 7%, respectively, for the erythromycin- and tetracycline-treated rats. These findings suggested that the metabolic activity of the intestinal flora is related to cancer induction by DMH. (Author abstract) (23 Refs)

37. EFFECTS OF CHRONIC ADMINISTRATION OF NEOMYCIN ON INTESTINAL CARCINOGENESIS IN THE AZOXYMETHANE (AOM)-TREATED-RAT MODEL (MEETING ABSTRACT).

Hamilton SR, Stephens RB, O'Ceallaigh D, Natuzzi E, Dick E, Boitnott JK, Baker RR, Yardley JH

Depts. of Pathology and Surgery, The Johns Hopkins Hospital, Baltimore, MD, 21205

Gastroenterology; 80(5,part2):1167 1981

Chronic oral administration of neomycin has been reported to promote experimental colon carcinogenesis. Effects of neomycin were studied in male Sprague-Dawley rats given 10 weekly sc injections of 14.5 mg/kg AOM, a potent bowel carcinogen, and killed 24 wk after first dose. Neomycin 0.5 mg/ml in distilled water was given as sole drinking fluid during the 10-wk course of AOM (WITH-AOM group), during the 14 wk after AOM was completed (POST-AOM), or for the full 24 wk (THRU-OUT). The CONTROL group receiv ed sc AOM and oral distilled water. Preliminary fecal bacteriologic studies showed that neomycin produced transient reduction in aerobic bacteria only. The two groups receiving neomycin after the course of AOM was completed (POST-AOM and THRU-OUT) showed a striking increase in both small and large bowel tumors. In contrast, administration of neomycin only during the course of AOM (WITH-AOM) increased small bowel tumors but caused no statistically significant increase in total colon tumors or actually decreased proximal colon tumors. Our findings confirm the promotion of experimental bowel carcinogenesis by chronic oral neomycin. Furthermore, they suggest that promotion in the colon occurred in mucosa rendered tumor-prone by previously administered AOM. Finally, the variability of effects, depending upon times of administration and portion of bowel studied, suggests that neomycin, which produced transient reduction of aerobic bacteria only, may effect carcinogenesis by mechanisms other than modification of fecal flora. (no Refs)

38. CARCINOGENIC FACTORS OF HEAD AND NECK CANCER (PART 1) - CLINICAL STUDY OF THE INFLUENCE OF SMOKING AND DRINKING.

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Nippon Jibiinkoka Gakkai Kaiho; 84(1):47-53 1981

Cigarette smoking and alcohol drinking histories of 140 patients (100 men, 40 women; 17-84 yr old) with malignant tumors were investigated. Sites of the tumors were the larynx in 44 patients, oral cavity in 34, pharynx in 29, tonsils or nasal cavity in 18, and thyroid in 15. Based on the strengths of the alcohols investigated (beer, Japanese sake, whiskey, shochu, wine, and vodka), a Shochu index was calculated (amount of shochu equivalent/day x number of yr drinking) for each patient, and the Brinkman index was used to indicate each patient's consumption of tobacco. Compared to the patients in other cancer groups, the patients with laryngeal cancer had high Brinkman indices (most were greater than 1,000) and Shochu indices (half were greater than 30). Tobacco smoking was the highest risk factor in laryngeal cancer, and the risk was markedly multiplied by alcohol consumption in supraglottic cancer. Drinking and smoking influenced the development of mesopharyngeal and piriform sinus cancers, and drinking influenced development of tongue and oral floor cancers, especially in men. Heavy smoking and drinking were believed to be high risk factors in development of head and neck cancers. (19 Refs) (In JPN)

39. PLASMA ZINC AND VITAMIN A IN HUMAN SQUAMOUS ESOPHAGEAL CANCER (MEETING ABSTRACT).

Mellow MH, Layne EA, Lipman TO, Kaushik M, Hostetler C, Smith JC

Veterans Administration Medical Center, Washington, DC, 20422

Gastroenterology; 80(5,part2):1229 1981

Experimental zinc deficiency in animals promotes esophageal tumor induction with chemical carcinogens. Retinoid administration has suppressed tumor progression in animals. Decreased plasma zinc and vitamin A have been noted in several human squamous cancers. We measured plasma zinc and vitamin A in alcoholic patients with newly diagnosed squamous esophageal cancer and compared these to three age-matched control groups: alcoholics without cancer; non-alcoholics with non-squamous cancer; non-alcoholics without cancer. Patients with factors thought to reduce plasma zinc or vitamin A were excluded: severe liver disease, severe protein energy malnutrition, infection, other acute illness. Conclusions: 1) Alcoholic patients with esophageal cancer have significantly decreased mean plasma zinc values compared to non-alcoholics without cancer. This is unlikely due to alcohol ingestion per se since 6 of 12 alcoholics without cancer had normal zinc values. This is also not due to the presence of a cancer since the non-alcoholics with cancer had normal zinc. 2) Patients with esophageal cancer as well as non-esophageal cancers had low mean plasma vitamin A. Our findings suggest a true deficiency of zinc and/or vitamin A nutrition in patients with esophageal cancer, which may have preceded the onset of illness. Zinc and/or vitamin A deficiency may contribute to the development of esophageal cancer. (no Refs)

REVIEWS

40. RECENT CONCEPTS OF INITIATION AND PROMOTION IN CARCINOGENESIS.

Becker FF
M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Am J Pathol; 105(1):3-9 1981

This review deals with premalignant liver lesions in rats fed N-2-acetylaminofluorene (AAF) or diethylnitrosamine (DEN), DNA alterations in premalignant lesions, and cellular responses to skin tumor promoters such as tetradecanoylphorbol acetate (TPA). Rats fed four cycles of AAF exhibited persistent hepatic nodules having increased mitotic activity and altered DNA. Similarly, premalignant lesions induced by DEN and phenobarbital showed an increase in altered DNA, which paralleled the increase in risk of hepatoma. The broad effects of tumor promotion consist of the induction of proliferation of an initiated cell population and the appearance of aggregates of altered cells. Tumor promoters such as TPA heighten the mitotic responses in these cells and eventually induce epigenetic programmatic alterations. (38 Refs)

41. CANCER PREVENTION - PRINCIPLES AND PROBLEMS.

Schramm T
Zentralinstitut fur Krebsforschung, Akademie der Wissenschaften der DDR, Lindenberger Weg 80, 1115 Berlin-Buch, E. Germany
Z Aerztl Fortbild (Jena); 75(11/12):526-529 1981

The general principles, approaches and problems in primary cancer prevention are discussed. The majority of all cancers in humans are caused directly or indirectly by exogenous factors. The major causes of cancer include tobacco, alcohol, sunlight, industrial chemicals, radiation, drugs, and possible factors determined by the life style. The existence of threshold doses for carcinogenic factors has not yet been clarified. The individual cancer risk is determined by the interplay of such processes as carcinogenesis, cocarcinogenesis, syncarcinogenesis, and anticarcinogenesis. The possibility of nitrosation of 61 drugs available in East Germany was investigated: slight nitrosation of ethambutol, piperazine, aminophenazone Analgin, desipramine, imipramine, clomipramine, ampicillin, oxacillin, and phenoxymethylpenicillin was determined. It was possible to inhibit but not completely suppress the nitrosation of these drugs by the addition of ascorbic acid. (22 Refs) (In GER)

42. METAL INTERACTIONS IN CARCINOGENESIS: ENHANCEMENT, INHIBITION.

Nordberg GF, Andersen O
Dept. Environmental Hygiene, Umea Univ., Umea, Sweden
Environ Health Perspect; 40:65-81 1981

The roles of metals in enhancing or inhibiting carcinogenesis are reviewed. Conclusive evidence of the carcinogenicity of arsenic has not yet been found, although some studies suggest it. Arsenic may act as a cocarcinogen. Selenium seems to be weakly mutagenic in bacteria and some mammalian cell cultures. Antitumor properties have been reported in experimental animals. Zinc is necessary as a trace element in the diet and may have anticarcinogenic effects. Nickel is strongly carcinogenic in experimental animals and humans. Its effects may be counteracted by manganese. Lead has not been confirmed as a carcinogen, but its presence in the environment warrants high priority research particularly on its effects in combination with other compounds. Chromium has been related to lung, and possibly stomach, cancer in man. Cadmium contributes to prostatic cancer and Leydig cell tumors. These effects can apparently be counteracted by zinc treatments. Carcinogenesis by benzo[a]pyrene, nitrosamines, and asbestos appear to be promoted by some metallic dusts. Further studies in vitro and in appropriate animal systems are urged. (155 Refs)

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CHEMICAL CARCINOGENESIS

1. CHEMICAL COMPOUNDS AND CANCER RISK.
Schramm T, Janisch W
Zentralinstitut fur Krebsforschung der Akademie der Wissenschaften der DDR, Lindenberger Weg 80, DDR-1115 Berlin, E. Germany
Arch Geschwulstforsch; 51(7):561-565 1981
In GER

2. THE CARCINOGENICITY OF ARSENIC.
Pershagen G
Dept. Environmental Hygeine, Karolinska Inst., Stockholm, Sweden
Environ Health Perspect; 40:93-100 1981

3. THE CARCINOGENICITY OF CHROMIUM.
Norseth T
Inst. Occupational Health, Gydas vei 8, Oslo 3, Norway
Environ Health Perspect; 40:121-130 1981

4. ROLE OF COBALT, IRON, LEAD, MANGANESE, MERCURY, PLATINUM, SELENIUM, AND TITANIUM IN CARCINOGENESIS.
Kazantzis G
TUC Centenary Inst. Occupational Health, London Sch. Hygiene and Tropical Medicine, Keppel St., London WC1E 7HT, England
Environ Health Perspect; 40:143-161 1981

5. RECENT RESEARCH ON NICKEL CARCINOGENESIS.
Sunderman FW
Dept. Lab. Medicine, Univ. Connecticut Sch. Medicine, Farmington, CT, 06032
Environ Health Perspect; 40:131-141 1981

6. ROLE OF CADMIUM IN CARCINOGENESIS WITH SPECIAL REFERENCE TO CANCER OF THE PROSTATE.
Piscator M
Dept. Environmental Hygiene, Karolinska Inst., S-104 01 Stockholm, Sweden
Environ Health Perspect; 40:107-120 1981

7. CHELATING AGENTS IN BIOLOGICAL SYSTEMS.
Schubert J
Dept. Chemistry, Univ. Maryland Baltimore County, Catonsville, MD, 21228
Environ Health Perspect; 40:227-232 1981

8. BENZENE AS A RISK FACTOR.
Stobbe H
Universitatsklinik fur Innere Medizin 'Theodor Brugsch', Bereich Medizin der Humboldt-Universitat, Schumannstrasse 20/21, DDR-1040 Berlin, E. Germany
Arch Geschwulstforsch; 51(7):575-578 1981
In GER

9. FORMALDEHYDE IN DENTISTRY: A REVIEW OF MUTAGENIC AND CARCINOGENIC POTENTIAL.
Lewis BB, Chestner SB
800-A Fifth Ave., Suite 503, New York, NY, 10021
J Am Dent Assoc; 103(3):429-434 1981

10. CARCINOGENICITY OF HYDANTOINS: DATA, HYPOTHESES, AND PUBLIC REVIEWS.
Scoville B, White BG
Natl. Inst. Neurological and Communicative Disorders and Stroke, NIH, Bethesda, MD, 20205
Psychopharmacol Bull; 17(3):195-197 1981

11. PHENOXY ACIDS, CHLOROPHENOLS, AND CANCER.
Hardell L, Eriksson M
Onkologiska kliniken, Regionsjukhuset, Umea, Sweden
Lakartidningen; 78(34):2862-2863 1981
In SWE

12. PHENOXY ACIDS: A BRIEF REVIEW OF THE POSSIBLE HYGIENIC EFFECTS.
Edling C
Yrkesmedicinska kliniken, Regionsjukhuset, Linkoping, Sweden
Lakartidningen; 78(34):2861-2862 1981
In SWE

DIETARY FACTORS IN CARCINOGENESIS

13. NUTRITIONAL MODULATION OF CANCER.
Nauss KM, Newberne PM
Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA, 02139
Cancer Detect Prev; 3(2):367-417 1981

14. FIBER CARCINOGENESIS: EPIDEMIOLOGIC OBSERVATIONS AND THE STANTON HYPOTHESIS.
Harington JS
Cancer Res. Dept., Natl. Cancer Assoc. South Africa, P.O. Box 2000, Johannesburg 2000, South Africa
JNCI; 67(5):977-989 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

15. EPIDEMIOLOGY.
Alderson MR
Dept. Epidemiology, Inst. Cancer Res., London, England
Recent Results Cancer Res; 78:1-19 1981

16. ATLAS OF CANCER MORTALITY IN THE PEOPLE'S REPUBLIC OF CHINA. AN AID FOR CANCER CONTROL AND RESEARCH.
Li JY, Liu BQ, Li GY, Chen ZJ, Sun XD, Rong SD
Dept. Cancer Epidemiology, Cancer Inst. Chinese Acad. Medical Sciences, 2, Yabao Lu, Chaoyang, Qu, Beijing, People's Republic of China
Int J Epidemiol; 10(2):127-133 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

17. SIXTH EAST GERMAN CANCER CONGRESS WITH INTERNATIONAL PARTICIPATION, BERLIN, MARCH 2-5, 1981.
Schramm T, Ebeling K, Schwarz R, Heise E, Glaser A, Tanneberger St, Anger G
No affiliation given
Arch Geschwulstforsch; 51(7):551-560 1981
In GER

18. EPIDEMIOLOGICAL STUDIES INTO THE POSSIBLE CARCINOGENICITY OF HAIR DYES.
Clemmesen J
(c/o P. Lohman), Medical Biological Lab. TNO., P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 87(1):65-79 1981

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

19. THE ROLE OF METALS IN CARCINOGENESIS: BIOCHEMISTRY AND METABOLISM.
Jennette KW
Dept. Chemistry, Dartmouth Coll., Hanover, NH, 03755
Environ Health Perspect; 40:233-252 1981

20. RECENT CONCEPTS OF INITIATION AND PROMOTION IN CARCINOGENESIS.
Becker FF
M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Am J Pathol; 105(1):3-9 1981

21. ACTIVATED METABOLITES OF CARCINOGENIC HYDROCARBONS.
Harvey RG
Ben May Lab., Univ. Chicago, Chicago, IL, 60637
Acc Chem Res; 14(7):218-226 1981

22. RELATIONSHIP BETWEEN METAL TOXICITY TO SUBCELLULAR SYSTEMS AND THE CARCINOGENIC RESPONSE.
Squibb KS, Fowler BA
Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC, 27709
Environ Health Perspect; 40:181-188 1981

23. ENZYMES INVOLVED IN THE REPAIR OF DAMAGED DNA.
Grossman L
Dept. Biochemistry, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 N. Wolfe St., Baltimore, MD, 21205
Arch Biochem Biophys; 211(2):511-522 1981

24. METAL-INDUCED INFIDELITY OF DNA SYNTHESIS.
Zakour RA, Kunkel TA, Loeb LA
Joseph Gottstein Memorial Cancer Res. Lab., Dept. Pathol., Univ. Washington, Seattle, WA, 98195
Environ Health Perspect; 40:197-205 1981

25. CHROMOSOME ABERRATIONS AND THEIR RELEVANCE TO METAL CARCINOGENESIS.
Vainio H, Sorsa M
Dept. Industrial Hygiene and Toxicology, Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
Environ Health Perspect; 40:173-180 1981

MODIFICATION OF CARCINOGENESIS

26. METAL INTERACTIONS IN CARCINOGENESIS: ENHANCEMENT, INHIBITION.
Nordberg GF, Andersen O
Dept. Environmental Hygiene, Umea Univ., Umea, Sweden
Environ Health Perspect; 40:65-81 1981

27. EFFECT OF METALS ON MUTAGENESIS AND DNA REPAIR.
Rossman TG
Inst. Environmental Medicine, New York Univ. Sch. Medicine, 550 First Ave., New York, NY, 10016
Environ Health Perspect; 40:189-195 1981

METHODOLOGY IN CARCINOGENESIS RESEARCH

28. SISTER CHROMATID EXCHANGES: A REPORT OF THE GENE-TOX PROGRAM.
Latt SA, Allen J, Bloom SE, Carrano A, Falke E, Kram D, Schneider E, Schreck R, Tice R, Whitfield B, Wolff S
Harvard Medical Sch., Boston, MA, 02115
Mutat Res; 87(1):17-62 1981

29. EFFECTS OF METALS IN IN VITRO BIOASSAYS.
Sirover MA
Dept. Pharmacology, Temple Univ. Sch. Medicine, Philadelphia, PA, 19140
Environ Health Perspect; 40:163-172 1981

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MODIFICATION OF CARCINOGENESIS

SERIES CK04 No. 82/04 APRIL, 1982

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MODIFICATION OF CARCINOGENESIS BY CHEMICAL AGENTS OR IRRADIATION

1. COMPARISON OF VARIOUS PROMOTING AGENTS ON THE INDUCTION OF PRENEOPLASTIC LESIONS IN THE RAT LIVER (MEETING ABSTRACT).

Ito N, Tsuda H, Hasegawa R, Imaida K
Nagoya City University Medical School, Nagoya 467, Japan
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Rats were injected ip with N-nitrosodiethylamine (DEN) or saline (control) as an initiator. Two wk after this, rats were given test compounds mixed in the basal diet or drinking water for six wk and then killed. The results show that administration of strong hepatocarcinogens such as aflatoxin B1, DEN, N-nitrosodimethylamine (DMN), 2-acetylaminofluorene (2-AAF), 3'-methyl-4-dimethylaminoazobenzene (3'-Me-DAB), thioacetamide, sterigmatocystin and ethionine resulted in large numbers of hyperplastic (neoplastic) liver nodules, whereas, dieldrin, dichloro-diphenyl trichloroethane (DDT), polychlorinated biphenyls, and alpha-hexachlorocyclohexane had less promoting effects. Non-hepatocarcinogens, such as N-nitrosoethylurea and 3-methylcholanthrene, also slightly enhanced the induction of hyperplastic nodules. Of the miscellaneous compounds tested, phenobarbital, deoxycholic acid and ethinyl estradiol enhanced the nodule induction. Hepatocarcinogens and chemicals with promoting activity in liver carcinogenesis gave positive results in this system. Thus our system could be used for screening hepatocarcinogens or hepatopromoters and also estimating their potency. (no Refs)

2. INHIBITION OF DENA-LIVER CARCINOGENESIS IN RATS WITH SODIUM OXYFERRISCORBONE.

Blagoeva PM, Balanski RM
Oncological Res. Inst., Medical Acad., Sofia, Bulgaria
Dokl Bolg Akad Nauk; 34(5):711-712 1981

Hepatocarcinogenesis induced in male BD/6 rats by nine weekly ip injections of diethylnitrosamine (80 mg/kg body wt) was reduced by 33% when animals were treated with a prophylactic regimen of sodium oxyferriscorbone (2 mg/kg body wt, ip five times per wk for 5 mo). It is suggested that sodium oxyferriscorbone may interfere with the oxidation-reduction processes in target tissues. (12 Refs)

3. QUANTITATIVE ASPECTS OF DRUG-MEDIATED TUMOR PROMOTION IN LIVER AND ITS TOXICOLOGICAL IMPLICATIONS (MEETING ABSTRACT).

Kunz HW, Schwarz M, Tennekes HA
The German Cancer Research Centre, Heidelberg, W. Germany
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Chronic exposure of rodents to high dose levels of drugs, food additives and environmental chemicals frequently results in liver enlargement. Several of these compounds have been found to enhance the incidence of liver tumors in animals briefly exposed previously to hepatocarcinogens. Accordingly, it has been advanced that these agents may act as tumor-promoters. These substances may also cause liver tumors in noncarcinogen-treated rodents, particularly in those characterized by a relatively high incidence of 'spontaneous' liver tumors. Since many of these chemicals are in common use, a crucial question would seem to be whether these effects are due to facilitation of the expression of pre-existing oncogenic potential. As a result of mechanistic differences tumor-promotion and syn-carcinogenesis must exhibit different dose-time-response characteristics, and accordingly, it should be possible, in principle, to discriminate between these phenomena. However, since tumor manifestation periods in the required lower dose-groups are likely to exceed the animals's av life-span, this approach is not feasible unless a sensitive early marker of carcinogenic activity can be employed. There is evidence that enzyme-deficient preneoplastic areas in liver can be used for this purpose. A strong quantitative correlation between carcinogen dose, the extent of enzyme deficient areas, and the subsequent appearance of tumors has now been established for a number of hepatocarcinogens, including those with weak initiating potential. On the basis of such quantitative analyses of the pre-neoplastic response several lines of evidence will be presented to indicate that liver-enlarging drugs do not act like solitary carcinogens, but function by facilitating the expression of carcinogenic potential. (no Refs)

4. THE ROLE OF GROWTH OF NORMAL AND PRENEOPLASTIC CELL POPULATIONS FOR TUMOR PROMOTION IN RAT LIVER (MEETING ABSTRACT).

Hermann RS, Schuppler J, Timmermann-Trosiener I, Ohde G
Institute of Toxicology and Pharmacology, Philipps-University, Marburg, W. Germany
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Studies in vivo on the mechanisms of tumor promotion provided the following results: 1) All liver tumor promoters identified so far stimulate growth of normal liver. 2) Hepatocytes in foci or islands of altered cells (putatively preneoplastic equals pn) show higher rates of replication than normal liver cells; various different liver tumor promoters cause a further increase of proliferation of focal cells. The increased proliferative activity is found in different island phenotypes and thus seems to be a useful marker of the putative preneoplastic state. 3) Early pn foci grow slowly without promotion despite the relatively high rates of cell replication. Promoters seem to accelerate island enlargement by increasing cell replication and decreasing cell necrosis. Tumor promotion thus appears to result from events that in principle are well known to occur in normal liver. 4) Putative pn foci of unknown ('spontaneous') origin are frequent in the liver of aged Wistar rats. They are morphologically and functionally (increased proliferation) very similar to those induced by carcinogens and are responsive to tumor promoters. Promotion of these 'spontaneous' foci may explain tumor appearance after long-term application of promoters. (no Refs)

5. ENHANCING EFFECTS OF DIMETHYLNITROSAMINE ON AFLATOXIN B1 HEPATOCARCINOGENESIS IN RATS.

Angsubhakorn S, Bhamarapravati N, Romruen K, Sahaphong S
Dept. Pathobiology, Faculty Science, Mahidol Univ., Rama 6 Road, Bangkok 4, Thailand
Int J Cancer; 28(5):621-626 1981

In a study of possible enhancing effects of dimethylnitrosamine (DMN) on aflatoxin B1 (AFB1) hepatocarcinogenesis, male Buffalo strain rats were fed diets containing 1 ppm AFB1, 25 ppm DMN, and a combination of 1 ppm AFB1 and 25 ppm DMN (AFB1 + DMN). The diets were replaced by chow pellets after 6 mo, and animals were killed 3, 6, 9 and 12 mo after

the onset of the experiment. In the untreated control group animals were free of hepatocellular carcinoma but the treated groups fed AFB1, DMN and AFB1 plus DMN developed hepatic lesions ranging from multiple cysts, altered cell foci and neoplastic nodules to hepatocellular carcinomas. Hepatocellular carcinomas developed in 79%, 45% and 5% of rats fed AFB1 plus DMN, AFB1 and DMN respectively at the end of the experiment. Multiple cysts were also found in all periods in animals fed AFB1 plus DMN, whereas rats fed AFB1 and DMN separately developed a few multiple cysts by the end of the experiment. These findings suggest that DMN potentiates the hepatocarcinogenesis induced by AFB1 in rats. (Author abstract) (28 Refs)

6. COMPARISON OF HEPATIC CARCINOGEN INITIATION-PROMOTION SYSTEM (MEETING ABSTRACT).

Leonard TB, Dent JG, Graichen ME, Popp JA
Chemistry Industrial Institute Toxicology, Research Triangle Park, NC, 27709
Toxicologist; 1(1):154 1981

A number of model systems have been designed to study the initiating and promoting phases of neoplastic development in rat liver. The purpose of these experiments was to determine if the promoting protocols alone altered liver biochemistry. Four protocols, which use the same initiator, diethylnitrosamine (DEN), but different promotional regimens, were investigated. The biochemical parameters evaluated were hepatic microsomal benzphetamine-N-demethylase (BPND), epoxide hydratase (EH), cytosolic DT-diaphorase, serum glutamic pyruvic transaminase (GPT) and serum gamma glutamyl transpeptidase (GGT) activities. The effect of initiation in these protocols was also evaluated to ascertain if DEN caused changes in liver biochemistry and if these changes were related to preneoplastic lesions. All 4 promoting regimes depressed BPND (20-50% of control) and all except one increased EH and DTD (3-fold). SGGT was elevated by all protocols (10x) but SGPT was only slightly changed. The combination of DEN initiation with promotion increased hepatic GGT positive foci (identified histochemically) but did not alter the biochemical parameters studied. We conclude that measurement of these enzymes is of no value for predicting neoplastic change. Ho wever, the data show that liver biochemistry, especially with respect to drug metabolism, is extensively altered by the promotional regimes. Consequently, study of promoter-induced changes in drug metabolizing enzymes may lead to a better understanding of biochemical events during promotion in hepatocarcinogenesis. (4 Refs)

7. TUMOR PROMOTION IN RAT LIVER (MEETING ABSTRACT).

Herren SL, Pereira MA
U.S. Environmental Protection Agency, Cincinnati, OH
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

An initiation/promotion bioassay using gamma glutamyl transpeptidase (GGTase) positive foci as the endpoint has been developed that can detect the carcinogenic potential of chemical carcinogens. GGTase-positive foci are presumed to be areas of initiated hepatocytes in contrast to the GGTase-positive areas of Zone 1 diffusion observed with compounds such as phenobarbital and saccharin. To evaluate the tumor promoting activity of phenobarbital, rats were administered diethylnitrosamine (DENA), 0.3 mmole/kg, followed by 500 ppm phenobarbital in their drinking water. After six wk of phenobarbital promotion, the rats had an increased incidence of foci as compared to non-phenobarbital treated rats. By 50 wk of phenobarbital promotion, the number of foci in the non-promoted animals equaled the number observed with promotion. This demonstrated that the initiator determined the ultimate number of foci while the promoter decreased the latent period required for the observation of foci. In an experiment to determine the effect of phenobarbital on the stability and progression of GGTase-positive foci, rats received a 2/3 partial hepatectomy, followed 24 hr later by DENA (0.3 mmole/kg). The rats then received 500 ppm phenobarbital in the drinking water for eight wk. After eight wk, half of the rats were continued on phenobarbital and the other half were taken off phenobarbital. The number of foci/cm 2 observed in rats continued on phenobarbital treatment leveled off after 10 wk of continuous promotion approached that observed with continuous phenobarbital promotion, while the number of foci/cm2 in the rats taken off phenobarbital initially decreased. However, 56 wk after the administration of DENA, the number of foci/cm2 from the rats removed from phenobarbital promotion approached that observed with continuous phenobarbital promotion, although the size of the foci from the rats on continuous promotion was larger. After 81 wk, all six (100%) of the rats on continuous promotion had liver tumors while only three of six (50%) rats removed from promotion had tumors. Therefore, continuous promotion by phenobarbital not only decreased the latent period for the appearance of foci, but also increased the s ize of DENA initiated foci as well as ultimately increasing the incidence of liver tumors. (no Refs)

8. EFFECTS OF PROMOTERS ON N-BUTYL-N-(4-HYDROXYBUTYL) NITROSAMINE INDUCED BLADDER CARCINOGENESIS IN THE RAT (MEETING ABSTRACT).

Ito N
Nagoya City University Medical School, Nagoya 467, Japan
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Male F344 rats were initially given 0.01% N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) for 4 wk in drinking water followed by the feeding of diet containing various chemicals for 32 or 34 wk. In the groups of animals subjected to sodium saccharin, sodium ascorbate, D,L-tryptophan and allopurinol, there was a significant increase in the incidence and number of papillary or nodular hyperplasias (PNH) compared to the groups given BBN alone. However, these compounds did not enhance the induction of papillomas which were generally considered to be more advanced lesions. Experiments were done to determine whether treatment with sodium saccharin or phenobarbital could enhance the neoplastic lesions in the bladder or liver of rats pretreated with 2-acetylaminofluorene (2-AAF) or BBN for initiation. Male Fischer 344 rats were given 0.05% phenobarbital and 5.0% sodium saccharin, respectively for 32 wk after 4 wk administration of hepatocarcinogens. Sodium saccharin significantly enhanced the induction of PHN in the bladder, but not of papillomas after BBN treatment, and significantly induced bladder hyperplasias after 2-AAF treatment. However, after 2-AAF or BBN treatment, an effect of phenobarbital for bladder and of sodium saccharin for liver neoplasia induction was not observed. The data indicate that although 2-AAF and BBN have tumor-initiating effects in both liver and urinary bladder, the tumor-promoting effects of phenobarbital and sodium saccharin are organ specific. (no Refs)

9. THE EFFECT OF PROMOTERS ON BLADDER CANCER INCIDENCE IN EXPERIMENTAL ANIMAL MODELS (MEETING ABSTRACT).

Hicks RM
Middlesex Hospital Medical School, London, England
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Multistage models of carcinogenesis have been proposed to account for the observed patterns of tumor development in the skin, liver, lung, bladder and other organs. Such models involve initiation of neoplastic change in a few cells by a threshold dose of carcinogen, followed by conversion of these latent tumor cells into an autonomous cancer by further doses of the same and/or other carcinogens, and/or non-carcinogenic promoting agents. In the rat urinary bladder neoplastic change can be initiated by a few wk treatment with low doses of N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) or N-(4-(5-nitro-2-furyl)-2-thiazolyl)formamide (FANFT) or by a single, low dose, intravesicular instillation of N-methyl-N-nitrosourea (MNU). Very few of the animals treated in such a way will develop bladder cancer in their natural life span unless, in addition, they are exposed subsequently to some further regime which will promote tumor growth from the initiated tumor cells. Many different factors will promote tumor growth in the initiated rat bladder including further low doses of complete bladder carcinogens, some dietary factors such as metabolites of tryptophan or deficiency of vitamin A, the food additives saccharin and cyclamate, and some alkylating agents such as cyclophosphamide and methylmethanesulphonate. Although promoters do not necessarily have all the attributes of complete carcinogens, and may not be mutagenic, by accelerating the process of tumor development and thus lowering the age-related cancer incidence in any particular population they may be of prime importance in regulating overall cancer statistics. (no Refs)

10. EFFECT OF REGENERATIVE HYPERPLASIA ON THE URINARY BLADDER: CARCINOGENICITY OF SODIUM SACCHARIN AND N-[4-(5-NITRO-2-FURYL)-2-THIAZOLYL]FORMAMIDE.

Cohen SM, Murasaki G, Fukushima S, Greenfield RE
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Cancer Res; 42(1):65-71 1982

The effect of ulceration of the urinary bladder on bladder carcinogenesis induced by N-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT) or sodium saccharin was evaluated in 5-wk-old F344 rats which were all killed 2 yr after the start of the experiment. The results indicate that long-term feeding of sodium saccharin, a nonmutagen, appears to be capable of inducing bladder tumors if administered to a rat with a proliferating bladder mucosa even without FANFT 'initiation.' Ulceration was induced by freezing. FANFT was fed at a level of 0.2% of the diet for 2 wk, and sodium saccharin was fed as 5% of the diet for 102 or 104 wk. Ulceration followed immediately by FANFT administration and then by control diet for 102 wk did not result in bladder tumors, whereas FANFT administration followed by ulceration and then control diet for a similar period induced bladder tumors. Ulceration followed by FANFT administration and then by 102 wk of sodium saccharin feeding induced bladder tumors, but ulceration followed by 2 wk of control diet followed by 102 wk of sodium saccharin feeding induced a similar incidence of tumors. Ulceration followed immediately by sodium saccharin (fed for 104 wk) induced a slightly lower incidence of tumors. FANFT followed by sodium saccharin without ulceration induced a single bladder carcinoma, but either chemical alone did not induce bladder tumors. Ulceration of the urinary bladder produced by a single ip inject ion of cyclophosphamide (100 mg/kg) gave similar results as ulceration by freezing. Ulceration alone induced by freezing or cyclophosphamide was followed by a reversible, regenerative nodular and papillary hyperplasia, and the bladder mucosa returned to normal in 3 to 4 wk after ulceration and remained normal through 2 yr. The lack of enhancing effect of FANFT, a potent mutagen, compared to control diet and ulceration induced by cyclophosphamide, a mutagenic alkylating agent, compared to ulceration induced by freezing support the hypothesis of carcinogenesis occurring without mutation. These results may also help to explain the carcinogenicity of sodium saccharin in two-generation and pellet implantation experiments and may assist in the identification of populations with increased susceptibility to bladder cancer. (Author abstract) (53 Refs)

11. PROMOTION IN URINARY BLADDER CARCINOGENESIS (MEETING ABSTRACT).

Cohen SM
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International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Aromatic amines, including, 2-naphthylamine, 4-aminobiphenyl, and benzidine, are known urinary bladder carcinogens in man and other species, but in rodents, aromatic amines and amides have usually induced liver tumors, occasionally also with tumors of the bladder and other tissues. Variations in organ specificity are related to differences in metabolism; for bladder the rates of acetylation and deacetylation appear to be critical. Bladder specific carcinogens in rodents and other species have subsequently been identified, including N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) administered in the drinking water, N-[4-(5-nitro-2-furyl)-2-thiazolyl] formamide (FANFT) in the diet and N-methyl-N-nitrosourea (MNU) instilled intravesically. When low doses of several baldder carcinogens (BBN, FANFT, 2-acetylaminofluorene, and 3,3'-dichlorobenzidine) are administered to rats, either simultaneously or sequentially, a synergistic effect is observed with respect to bladder carcinogenesis. In addition, multistage carcinogenesis has been demonstrated in rats for the bladder using MNU or FANFT as initiators, and sodium saccharin, sodium cyclamate, or tryptophan in the diet as promoters. The urothelium normally has a very low mitotic rate. If mucosal proliferation is increased, such as during fetal development or during regeneration and repair of an ulcer, the bladder appears to be considerably more sensitive to the effects of promoting substances. For example, if sodium saccharin is administered to rats after ulceration of the bladder, even without prior administration of an initiator, bladder carcinoma develops. Under these conditions, the substance appears as a carcinogen. Human populations with increased bladder epithelial proliferation, such as the fetus, infants, patients with bacterial cystitis, or men with partially obstructive prostatism, may have increased susceptibility to the action of carcinogenic or promoting stimuli. (no Refs)

12. TUMOR PROMOTERS AND COCARCINOGENS IN TOBACCO CARCINOGENESIS (MEETING ABSTRACT).

Hoffmann D, Hecht SS, Wynder EL

American Health Foundation, Valhalla, NY

International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Cigarette smoke induces carcinoma of the larynx in Syrian golden hamsters and is active as a tumor promoter in hamsters pretreated with a low dose of a polynuclear aromatic hydrocarbon, nitrosamine, or nitrosamide. These tumorigenic effects are only observed with total smoke, but not with the gas phase alone. This demonstrates that the tumorigenic agents reside primarily in the particulate phase. According to fractionation experiments, a number of four- and five- ring aromatic hydrocarbons serve as the major tumor initiators in tobacco smoke. Tumor promoters reside primarily in weakly polar neutral subfractions and in the weakly acidic portion of the particulate matter and include certain unsaturated hydrocarbons and phenolic compounds. Cocarcinogenic activity is a characteristic feature of tobacco smoke and its particulates. Among the cocarcinogens formed during combustion are catechols and certain non-tumorigenic aromatic hydrocarbons and terpenes. Nicotine may also serve as a cocarcinogen as is indicated by preliminary data. The presentation will discuss the action of tumor promoters and cocarcinogens in tobacco carcinogenesis, the precursors for tobacco smoke promoters and cocarcinogens, and methods for their reduction in smoke. (no Refs)

13. COCARCINOGENICITY OF FOUNDRY PARTICULATES (MEETING ABSTRACT).

Niemeier RW, Stettler LE, Mulligan LT, Rowland J

No affiliation given

Second Annual NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Cancer Studies, September 9-11, 1981, Rockville, Maryland. National Cancer Institute 33 pp., 1981.

The traditional use of silica sand for metalcasting is slowly being replaced by non-silica aggregates due to increased demands for improved cast surfaces and closer dimensional tolerances, and due to the physical, chemical and biological limitations of silica sands. The major non-silica aggregates presently used throughout the metalcasting world include zircon sand, olivine sand, chromite sand and aluminum silicates. However, little is known about the biological effects of these materials. The sands are currently being evaluated for both fibrogenic and cocarcinogenic potential in the hamster model by intratracheal administration of the commercial sand with or without concurrent administration of benzo(a)pyrene (BaP). Respirable fractions of the sands were prepared either by sieving and/or air classification or by micronizing. Particle size analyses of the respirable fractions showed that more than 99% of each sample was less than 10 um and that surface areas varied from 1.01 to 2.41 m(2)/g. Free silica contents of the nonsiliseous sands were all found to be less than 1%. Chrysotile asbestos were found in both olivine samples and chromite sand. Amphibole fibers were also found in the latter. The study is designed so that the final sacrifice will occur 90 wk from the start of exposure. Interim results are reported here and show that lung tumors have been found in all groups receiving the aggregate plus B(a)P, but no lung tumor bearing animals have been found in the aggregate only groups. The relative severity of the fibrogenic and carcinogenic responses must await final histopathological examination and statistical analyses. (no Refs)

14. PROMOTION OF LUNG TUMORS IN MICE (MEETING ABSTRACT).

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International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Experimental evidence obtained during the last 6 yr shows that several elements of two-stage carcinogenesis apply to the development of lung tumors in Strain A or Swiss-Webster mice. At least three agents which have been identified as promoters in skin, urinary bladder, and liver will also enhance tumor formation in lung: phorbol, saccharin, and butylated hydroxytoluene (BHT). The antioxidant BHT acts in many respects like a typical promoting agent: it is effective if animals are treated after exposure to an initiating agent, but not if tney are treated beforehand. Administration of BHT can be delayed up to 5 mo after urethan treatment and still enhance tumor formation. BHT enhances lung tumor formation regardless of its route of administration (ip injection, gavage, or ingestion in the diet). The lowest dose of BHT required to produce an effect has not yet been determined. In at least one mouse strain, BHT also enhances tumor formation in animals initiated with 3-methylcholanthrene or diethylnitrosamine. On the other hand, no evidence is available yet to show that BHT would enhance tumor development in animals treated with subcarcinogenic doses of an initiating compound. Nor has it been possible to produce more tumors with BHT in mouse strains which have a low spontaneous tumor incidence and respond poorly to urethan. The question has not been resolved whether BHT accelerates growth of preformed tumors only or whether it induces the formation of more tumors. (no Refs)

15. INFLUENCE OF NITROGEN DIOXIDE OR FORMALDEHYDE ON INCIDENCE OF DIETHYLNITROSAMINE-INDUCED TUMORS IN HAMSTER RESPIRATORY TRACT (MEETING ABSTRACT).

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Toxicologist; 1(1):138 1981

The potential enhancing activity of two model irritant gases, nitrogen dioxide and formaldehyde, on chemically induced tumors in the respiratory tract was investigated. Adenomas were produced throughout the respiratory tract of male Syrian golden hamsters by 10 weekly sc injections of 0.5 mg of diethylnitrosamine (DEN). Hamsters also received weekly 5-hr exposures to either nitrogen dioxide (10 ppm) or formaldehyde (30 ppm). Gas exposures were begun either concurrently with DEN (a single exposure 48 hr prior to each DEN injection) or two wk after the last DEN injection. Gas exposures continued for lifetime. DEN treatment increased mortality above that of untreated controls; formaldehyde exposures of DEN-treated hamsters increased mortality further. Tumor incidence was evaluated on a subgross level after staining and clearing of whole organs of the respiratory tract. Histologic sampling of observed lesions verified this method of scoring tumors. The number of tumor bearing animals (TBA) was not increased by irritant gas exposures of DEN-treated hamsters, but the number of tumors per TBA was significantly increased by exposure to formaldehyde concurrent to DEN treatments. (no Refs)

16. PYRAN COPOLYMER AND 7,12-DIMETHYLBENZANTHRACENE-INDUCED CARCINOGENESIS IN THE HAMSTER CHEEK POUCH.

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Arch Oral Biol; 26(10):761-767 1981

The anticarcinogenic action of pyran copolymer (PC) on 7,12-dimethylbenzanthracene (DMBA)-induced carcinogenesis in the cheek pouch of male Golden Syrian hamsters was examined. All hamsters treated topically with DMBA exhibited buccal pouch tumors after 11 wk. None of the animals receiving no treatment (Group 1) or mineral oil alone (Groups 2 and 4) developed tumors. Group 3 (saline- and DMBA-treated) and Group 5 (PC- and DMBA-treated) hamsters displayed mean tumor latent periods of 7.900 and 8.074 wk, respectively. Groups 3 and 5 exhibited mean tumor diameters of 2.7 and 3.0 mm, respectively, at 11 wk. Groups 1-4 included 6 hamsters each; Group 5 was composed of 24 hamsters. One hamster each in groups 1, 2, 3, and 5 died prior to the end of the 11-wk period. No significant difference in carcinoma incidence was observed between Groups 3 and 5 after 11.5 wk. Of Group 3 and 5 hamsters, 100% and 96%, respectively, developed carcinomas. No consistent difference in histologic appearance of carcinomas was observed between Groups 3 and 5. Mean hemagglutinin titers were higher in groups receiving PC than in the saline-treated control groups, but the difference was not significant. Analysis of immunologic findings for Groups 3 and 5 demonstrated a statistically significant difference in respective mean titers ($p = 0.01$). Organ and blood-cell changes were noted only in PC-treated animals. The results indicated that PC had little if any effect on DMBA-mediated buccal pouch carcinogenesis. (27 Refs)

17. MORPHOMETRIC INVESTIGATIONS INTO THE EFFECTS OF VITAMIN A ON HAMSTER CHEEK POUCH CARCINOGENESIS (MEETING ABSTRACT).

White FH, Al-Azzawi B
Department of Human Biology and Anatomy, University of Sheffield, Sheffield, England
Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

There are at present few histological reports which describe quantitative alterations of tissue architecture which occur during neoplastic development. This work comprises part of an extensive investigation at both light and ultrastructural levels which attempts to quantify abnormalities of tissue architecture during experimental carcinogenesis and its treatment using morphometric procedures. After application of dimethylbenzanthracene (DMBA) to cheek pouches, material was collected at 6, 9, 12 and 16 wk intervals and processed for light microscopical examination. These samples included a spectrum of premalignant lesions. A second group of animals received topical application of 5% vitamin A palmitate in corn oil three x per wk following induction of the first neoplasms. After appropriate sampling the vol density of epithelium (VVEP) and the vol density of blood vessels (VVBV) were quantified using a MOP-AMO3 semi-automatic image analyzer. At 16 wk, ie after approx 5 wk of vitamin A treatment, values of VVEP and VVBV were significantly lower than in animals treated with DMBA alone. These results, when correlated with regressive changes in macroscopical and histological appearances of the lesions, suggest that the tumor cell component is decreasing in proportion to the adjacent connective tissue and that a significant feature in tumor regression is a decreased vascularity of the lesions. The mechanisms governing these alterations and their specificity await elucidation, but on the basis of our results, morphometry may provide a valuable tool in biological and clinical studies of cancer therapy. (no Refs)

18. THE EFFECT OF DISULFIRAM ON THE CARCINOGENICITY OF 3,2'-DIMETHYL-4-AMINOBIPHENYL IN SYRIAN GOLDEN HAMSTERS AND RATS.

Fiala ES, Weisburger JH, Katayama S, Chandrasekaran V, Williams GM
Naylor Dana Inst. for Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Carcinogenesis; 2(10):965-969 1981

Species differences in 3,2'-dimethyl-4-aminobiphenyl (DMAB) carcinogenicity, which induces mostly bladder tumors in Syrian hamsters and intestinal and breast tumors in rats, were investigated. Groups of male Syrian golden hamsters received sc injections of DMAB weekly for up to 22 mo (total av cumulative dose 555 mg) either alone or simultaneously with disulfiram in the diet. At the tolerated dose of disulfiram (2.5 mg/kg), the overall tumor yield induced by DMAB alone was not affected, but the number of small intestine tumors was reduced and the appearance of bladder and colon cancers was delayed. In two groups of male Charles River rats, weekly sc injection of DMAB (20 mg/kg) for 37 wk (total av cumulative dose 289 or 241 mg) induced primarily intestinal cancers. As in hamsters, addition of disulfiram to the diet of the second group reduced the incidence of small intestine cancers but resulted in the appearance of a small number of bladder cancers. DMAB-treated rats also developed in situ prostatic carcinoma, regardless of whether they were treated with or without disulfiram. (19 Refs)

19. INHIBITION OF PANCREATIC CARCINOGENESIS BY RETINOIDS IN AZASERINE-TREATED RATS.

Longnecker DS, Curphey TJ, Kuhlmann ET, Roebuck BD
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Cancer Res; 42(1):19-24 1982

Chemoprevention by retinoids of the progression of carcinomas induced in rats by azaserine was evaluated. Wistar/Lewis rats were given 15 weekly injections of azaserine, 10 mg/kg, while fed a chow diet; after the completion of carcinogen treatment, they were fed a chow diet supplemented with four different retinoids at the level of 0.5 to 2 mmol/kg diet for 1 yr. The incidence of neoplasms was determined by autopsy and histological study. The incidence of pancreatic carcinoma among a male positive control group (azaserine treated, but not retinoid treated) was 42%. The incidence of pancreatic carcinoma among male rats treated with retinoids was: N-2-hydroxyethylretinamide, 6%; N-4-propionyloxyphenylretinamide, 17%; and retinylidene dimedone, 12%. The incidence in rats fed these three retinoids was significantly (p less than 0.05) below the control group incidence. Thus, these three retinoids appeared to be effective in inhibiting the progression of pancreatic carcinomas in the azaserine-induced model. A similar trend was demonstrated in females, but statistical significance was shown only in rats fed N-2-hydroxyethylretinamide. A fourth retinoid, N-4-carboxyphenylretinamide, was more toxic and less effective in chemoprevention. Since retinoids were fed after exposure to carcinogen, the effect was exerted during the postinitiation phase of carcinogenesis. The ratio of invasive pancreatic carcinomas to localized carcinomas (carcinoma in situ) was clearly

higher among non-retinoid-treated rats than among those treated with retinoids. This is consistent with retarded progression in the retinoid-treated groups. (Author abstract) (10 Refs)

20. EFFECT OF CAFFEINE (CF) ON PANCREATIC CARCINOGENESIS OF 4-HYDROXYAMINO-QUINOLINE 1-OXIDE (4-HAQO) IN RATS (MEETING ABSTRACT).

Konishi Y, Denda A, Yokose Y, Takahashi S
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Newsletter Natl Pancreas Cancer Project; VI(2):31 1981

Sixty male Wistar rats weighing 160 g were used. 4-HAQO, at a dose of 7 mg/kg was given by iv injection and CF was given by sc injection for 12 hr intervals. Group (G) 1 received 4-HAQO at 3 days after partial pancreatectomy (PP) G 2 received 6 x injections of 120 mg/kg of CF before 4-HAQO which was given 3 days after PP. Gs 3, 4, and 5 received 12 x injections of 120, 60, and 30 mg/kg of CF after 4-HAQO which was given 3 days after PP, respectively. All rats were sacrificed at 52 wk, and examined macroscopically and histologically. The numbers of pancreatic tumors counted macroscopically were 14.9 +/-6.6 in G 1, 10.0 +/-5.9 in G 2, 6.0 +/- in 3.2 G 3, 22.7 +/-8.3 in G 4, and 28.1 +/-11.4 in G 5. These results suggest that CF showed biphasic effects, inhibitory and enhancing ones, on the pancreatic carcinogenesis of 4-HAQO in rats. (no Refs)

21. INHIBITORY EFFECT OF 4,4'-DIAMINODIPHENYLMETHANE ON LIVER, KIDNEY AND BLADDER CARCINOGENESIS IN RATS INGESTING N-ETHYL-N-HYDROXYETHYLNITROSAMINE OR N-BUTYL-N-(4-HYDROXYBUTYL)NITROSAMINE.

Fukushima S, Hirose M, Hagiwara A, Hasegawa R, Ito N
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Carcinogenesis; 2(10):1033-1037 1981

Effects of 4,4'-diaminodiphenylmethane (DDPM) in the 'post-initiation' stage of liver, kidney, and bladder carcinogenesis induced in male F344 rats by N-ethyl-N-hydroxyethylnitrosamine (EHEN) or by N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) were investigated. Rats given 0.1% EHEN in drinking water for 2 wk followed by DDPM treatment (0.1% in diet, 32 wk) had significantly fewer renal neoplastic nodules (av 0.28/square cm [cm2]) and renal cell tumors (av 0.16/cm2) than rats treated with EHEN alone (1.88 neoplastic nodules and 0.51 renal cell tumors/cm2). DDPM did not inhibit development of hyperplastic nodules in the liver. However, hepatocellular carcinomas did not occur in rats treated with EHEN and DDPM, whereas they were observed in 7/21 rats treated with EHEN alone. DDPM (0.1% in diet, 34 wk) also reduced the frequency of bladder papillomas induced by 4 wk or BBN treatment (0.01% in drinking water). In these experiments, rats treated with DDPM showed growth retardation and decreased food intake. (25 Refs)

22. CARCINOGENICITY OF INHALED 1,2-DIBROMOETHANE IN RATS TREATED WITH DISULFIRAM (MEETING ABSTRACT).

Wong LC, Winston JM, Hong CB
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Toxicologist; 1(1):130 1981

A chronic inhalation study of ethylene dibromide (EDB) was conducted in Sprague Dawley rats. The study consisted of four groups of rats receiving control air and control diet, 20 ppm of EDB and control diet, control air and 0.05% of disulfiram (DS) in the diet, and 20 ppm of EDB and 0.05% of DS in the diet, over a period of 18 mo. Rats receiving 20 ppm of EDB showed high mortality and an increase in tumor incidences in mammary glands, spleen, adrenals, liver, kidneys, and sc tissues. A combination of 20 ppm of EDB and 0.05% DS in the diet caused earlier deaths and high mortality rate, decreases in body wt gain, food consumption, Hb, hematocrit and RBC counts in rats. This combination of EDB and DS treatment also caused early development and high incidences of tumors in liver, spleen, kidneys, adrenals, thyroids, lungs, mesentary and mammary tumors. In addition, 90% of male rats that received a combination of EDB and DS treatment had testicular atrophy. Addition of DS treatment caused early deaths and high mortality rate, and promoted not only the tumor incidences in various organs and tissues in both male and female rats, but also the testicular atrophy in rats. (no Refs)

23. MODIFICATION OF THE CARCINOGENIC PROCESS IN COLON CANCER BY ENDOGENOUS AND EXOGENOUS FACTORS (MEETING ABSTRACT).

Daugherty JP
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International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

The United States has one of the highest rates of colon cancer in the world, and the incidence and survival rates have changed little in the last 30 yr. There are several areas of responsibility in dealing with the health aspects of tumor promotion in colon carcinogenesis. The first of these involves an understanding of cancer epidemiology. Numerous epidemiological studies have implicated a variety of exogenous and endogenous factors in the etiology of human colon cancer. These factors have been demonstrated to influence numerous biochemical parameters by reacting with biomolecules, changing the transit time and vol of fecal material and altering intestinal microflora. The second area involves basic experimental investigations to determine the validity of the associations suggested by epidemiological findings. The development of screening methods for those individuals with a high risk for the development of colon cancer, as well as screening for potential carcinogens and modifiers of carcinogenesis is a third area of concern. A fourth area of concern is inhibition of the carcinogenic process. It is apparent that the best way to reduce the incidence of cancer is to prevent exposure to carcinogens. However, it is rarely possible to reduce or eliminate human exposure to cancer-causing agents, and it is necessary to approach cancer prevention by the use of agents which inhibit cancer formation. Since carcinogenesis is a prolonged, multistage process, a variety of approaches exist for inhibition of the carcinogenic process, either at the state of initiation, cocarcinogenesis or promotion. Finally, the possible role of therapeutic agents in the development of colon cancer should be examined especially in view of the alterations which these agents produce in the concentration and/or type of bile acid and cholesterol metabolites in the colon as well as alterations in various other agents. (no Refs)

MODIFICATION OF CARCINOGENESIS BY DIETARY COMPONENTS OR DIGESTIVE FACTORS

24. BILE ACIDS, BUT NOT NEUTRAL STEROLS, ARE TUMOR PROMOTERS IN THE COLON IN MAN AND IN RODENTS (MEETING ABSTRACT).

Weisburger JH, Reddy BS, Wynder EL

American Health Foundation, Valhalla, NY

International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Colon cancer in man has distinct incidence patterns in various parts of the world. The key element distinguishing high and low populations is the intake of dietary fat and fiber. The mechanism whereby dietary fat operates in colon carcinogenesis is through control of endogenous cholesterol biosynthesis which, in turn, is the source of bile acid synthesis in the liver. Bile acids are secreted into the intestinal tract. Primary, and more so secondary bile acids were shown to be colon tumor promoters in several lines of experimentation. Dietary fat, thus, leads to specific total bile acid flow through the intestinal tract, accounting for a promoting effect. Fiber, especially cereal fiber, determines stool bulk which exerts a diluting effect on the total bile acid level in the tract. The concentration of bile acids at the mucosal barrier effectively relates to the extent of promoting action. Those findings have been made in man and animal models, thus strengthening the mechanistic concept underlying colon carcinogenesis. In most areas of the world levels of dietary fat and cholesterol relate to the risk for colon cancer and also for coronary heart disease, the latter through determining the amount of total serum cholesterol and of high density lipoprotein cholesterol. Recent instances of low serum cholesterol and apparent high colon cancer risk are accounted for by our findings, namely a higher conversion of cholestrol to bile acids acting as tumor promoters. Protection in such cases can be readily secured by ensuring an adequate intake of cereal fibers. (no Refs)

25. EFFECT OF BILE ACID GAVAGE OR VAGOTOMY AND PYLOROPLASTY ON GASTROINTESTINAL CARCINOGENESIS.

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Am J Surg; 142(5):551-554 1981

Possible promotion of MNNG-induced gastrointestinal carcinogenicity was evaluated in male Wistar rats exposed to unconjugated bile acid given as gavage or as obtained through truncal vagotomy plus pyloroplasty. No significant difference was found compared with the relevant control groups. Even though gastroduodenal erosions were found more frequently in the bile acid gavage and MNNG groups than in MNNG-treated controls, secondary deconjugated bile acids apparently did not reach optimal promoting concentrations. In contrast to partial gastrectomy, vagotomy and pyloroplasty do not increase the tumor yield in the rat. (Author abstract) (23 Refs)

26. TUMOR PROMOTION OF THE GASTROINTESTINAL TRACT OF ANIMALS: DIETARY FACTORS (MEETING ABSTRACT).

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International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

The biological mode of action of tumor promoters exemplified by the phorbol esters, is a subject of intensive study in a number of laboratories. A few investigators have recently begun to examine the role of dietary nutrients in tumor promotion, but the available data are sparse and interpretation difficult. A few examples are provided to indicate that some nutrients may be important in the promotion of cancer. However, the fine dividing line between effects on initiation or on promotion, so clearly shown in the mouse two-stage skin cancer model, is not so clear as yet in models used for studies in nutritional carcinogenesis. The animal models for these studies have been primarily rats, mice and hamsters. These have shown that nutrients which appear to have promotion activity are zinc deficiency and 13-cis-retinoic acid for the esophagus; vitamin A deficiency for liver and colon, lipotrope deficiency for the liver; selenium for the liver. It is probably more correct at this early stage of investigation to consider the effects of nutrients acting either during the time of administration of the carcinogen or, after such administration and when no detectible carcinogen is found in the animals tissues, rather than as promoters in the strict sense. (no Refs)

27. OCCURRENCE OF LARGE INTESTINE CANCER AND THE ROLE OF INTRALUMINAL BACTERIA.

Hirono I

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Nippon Rinsho; 39(5):32-35 1981

Intestinal bacteria convert some of the free bile acid released into the small intestine eventually from chenodeoxycholic acid, deoxycholic acid, lithocholic acid, etc into secondary bile salts that have effects as promoters of large intestinal tumor growth. When large amounts of fats are consumed, more bile salts are released into the small intestine, and a greater amount of bile salts are potentially not reabsorbed for reuse in the liver; thus, the unabsorbed bile salts that travel into the large intestine are converted into potential carcinogenic promoters by the bacteria. The bacterial flora in the intestine and frequency of cancer of the large intestine varies according to geographic location, suggesting a causal link. Bacteria in the transverse colon can produce N-nitrosamine compounds from amines and nitric acid that is not excreted in the urine. However, if the fiber content of the feces is sufficient, the feces moves rapidly through the large bowel and direct contact of the carcinogens with the luminal wall is minimal. Roles of various types of bacteria in production of other large intestinal carcinogens have been shown, but explanations of the carcinogenic mechanisms are still being investigated. (14 Refs) (In JPN)

28. THE TWO-GENERATION SACCHARIN BIOASSAYS (MEETING ABSTRACT).

Arnold DL
Health Protection Branch, Ottawa, Canada
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Saccharin was discovered over 100 yr ago and the controversy regarding its safety for human consumption started shortly therafter and has not subsided appreciably in the intervening decade. The consumption of saccharin, particulary in North America, started to escalate when under new standards of identity, the US Food and Drug Administration allowed foods containing artificial sweeteners to be promoted as 'nonnutritive' or 'noncaloric' sweeteners for use by the general public. In 1969, when cyclamates were banned, at least 10 single generation feeding studies were undertaken to more accurately assess the toxicological consequences resulting from the anticipated increased consumption of saccharin. While none of these studies resulted in any overt regulatory action, the introduction of the two-generation chronic toxicity/carcinogenicity bioassay added a new total to the toxicologists' arsenal. Three studies have since been conducted using the protocol, and the results from these studies clearly show that when rats were exposed to diets containing 5 or 7.5% sodium saccharin from the time of conception to death, and increased frequency of urinary bladder cancers were predominately found in the males. While some study results suggested that impurities in commercial saccharin, or the presence of urinary tract calculi may have been responsible for the observed bladder tumors, it now appears that these possibilities are highly unlikely. The mechanisms by which saccharin elicited the bladder tumors using the two-generation experimental model has not been ascertained. (no Refs)

29. COCARCINOGENICITY BY SACCHARIN OF HEPATOCARCINOGENICITY (MEETING ABSTRACT).

Pereira MA
U.S. Environmental Protection Agency, Cincinnati, OH
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

We have demonstrated that sodium saccharin was cocarcinogenic towards dibutylnitrosamine (DBN) hepatocarcinogenesis. The simultaneous administration of 5% sodium saccharin in the diet and 0.02% DBN in the drinking water of male rats for 26 wk resulted in a significant increased incidence of preneoplastic foci, hyperplastic nodules and hepatocellular carcinomas compared to rats that received only DBN. The liver of the rats receiving both DBN and saccharin also had an increased incidence of gammaglutamyltranspeptidase (GGTase) positive foci after 4, 8 and 26 wk of treatment. The size distribution of the GGTase-positive foci was the same in the livers of the DBN and DBN-saccharin groups. The livers from rats that only received saccharin did not contain GGTase-positive foci but rather contained at 4 to 8 but not 26 wk a large number of GGTase-positive hepatocytes in Zone 1. It would appear that by 26 wk of saccharin treatment the liver may have developed resistance to saccharin. Our results indicate that the mechanism for the cocarcinogenic activity of saccharin involves an increase in the amount of initiated GGTase-positive foci, and by implication initiation sites of carcinogenesis rather than an increased growth rate of GGTase-positive foci. This implies that the cocarcinogenic activity of saccharin in the liver involves a mechanism different from tumor promoters which act to increase the rate of progression (growth) from the initiated cell to the appearance of cancer. (no Refs)

30. MODULATION OF TUMOR PROMOTION IN LIVER CARCINOGENESIS (MEETING ABSTRACT).

Shinozuka H, Abanobi SE, Lombardi B
University of Pittsburgh School of Medicine, Pittsburgh, PA
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Earlier, we demonstrated that feeding to rats a diet devoid of choline, a lipotrope factor, markedly enhances hepatoma induction by several chemical carcinogens, and that the diet acts as a strong promoter of liver carcinogenesis. Several modulating factors, which influence the efficacy of the choline-devoid (CD) diet as a promoter, were investigated by quantitating the evolution of initiated liver cells to foci of gamma glutamyltranspeptidase-positive hepatocytes. The addition to the CD diet of phenobarbitol (PHB) resulted in a promoting action stronger than those of the CD diet or PHB alone. Two structural ly similar barbiturates, amobarbital and pentobarbital exerted an effect similar to that of PHB, while barbituric acid, the basic moiety of barbiturates, had no effect. In other studies, lowering of the fat content of the CD diet reduced its efficacy as promoter, while the addition of a hypolipidemic agent, BR931 4-chloro-6-(2,3 xylidino)-2-pyrimidinylthio(N-B-hydroxy ethyl) acetamide completely abolished the promoting action of the CD diet. Feeding the CD diet caused a marked enhancement of liver DNA synthesis and cell proliferation relative to those in rats fed the choline supplemented diet. The effects of various modulating factors on the CD diet mediated cell proliferation are being studied, and the possible significance of liver cell proliferation as a mechanism of tumor promotion will be discussed. (no Refs)

31. INHIBITORY ACTION OF ASPARAGUS RACEMOSUS ON DMBA-INDUCED MAMMARY CARCINOGENESIS IN RATS.

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Cancer Biology Lab., Sch. Life Sci., Jawaharlal Nehru Univ., New Delhi-110 067, India
Int J Cancer; 28(5):607-610 1981

The present paper reports the inhibitory effect of Asparagus racemosus on DMBA-induced mammary tumorigenesis in rats of Holtzman strain. When virgin female rats, normal or primed with 17-beta-estradiol treatment, are put on diets containing 0.25%, 0.5%, 1% or 2% Asparagus root extract powder prior to their exposure to DMBA, mammary tumor incidence shows a sharp decline. (Author abstract) (39 Refs)

32. EFFECT OF BETA-GLUCURONIDASE INHIBITOR ON AZOXYMETHANE-INDUCED COLONIC CARCINOGENESIS IN RATS.

Takada H, Hirooka T, Hiramatsu Y, Yamamoto M
Dept. Surgery, Kansai Medical Univ., 1 Fumizono, Moriguchi, Osaka, Japan
Cancer Res; 42(1):331-334 1982

In this study of the role of microfloral beta-glucuronidase in colonic carcinogenesis, the effect of beta-glucuronidase inhibitor was evaluated. Starting at 5 wk of age, male Donryu rats were fed either a semisynthetic diet or the same diet containing 0.1% beta-glucuronidase inhibitor as N-cyclohexyl-5-O-acetyl-2,4-O-(p-methoxybenzylidene)-D glucaro-1-amide-6,3-lactone (C-GAL). All animals were given sc injections of 7.4 mg azoxymethane (AOM) per kg body wt once a wk for 11 wk and followed for an additional 20 wk. Most animals receiving the colonic carcinogen developed tumors in the colon, and a few

also developed tumors in the small intestine. However, the number of tumors in the large intestine of the rats given C-GAL at the same time as AOM was significantly lower than in the control rats, especially in the proximal half of the colon, but those given C-GAL after AOM treatment had almost the same number of colon tumors as did the controls. It is concluded that, since bacterial beta-glucuronidase activity in the feces of rats given 0.1% C-GAL was significantly inhibited, intestinal microfloral beta-g lucuronidase may play an important role in colonic carcinogenesis caused by AOM. (Author abstract) (48 Refs)

MODIFICATION OF CARCINOGENESIS BY HORMONAL OR GENETIC FACTORS

33. INFLUENCE OF PROLACTIN AND GROWTH HORMONE ON RAT MAMMARY TUMORS INDUCED BY N-NITROSOMETHYLUREA.

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Cancer Res; 42(1):35-38 1982

The effects of hypophysectomy and prolactin-suppressing drugs on the growth of mammary tumors induced in Sprague-Dawley rats by N-nitrosomethylurea and dimethylbenz(a)anthracene were compared. The influence of ovine prolactin and growth hormone administration on N-nitrosomethylurea-induced tumors was also studied in hypophysectomized animals. After hypophysectomy, all 13 tumors induced in 13 rats by N-nitrosomethylurea underwent regression, as did 10 of 12 induced by dimethylbenz(a)anthracene. There were no new tumors. Pergolide mesylate, a long-acting ergoline derivative, was given in a dose of 80 ug bid by sc injection for 28 days. Only 3 of 12 N-nitrosomethylurea-induced tumors regressed, while 4 became static. However, only two new tumors developed in the 12 pergolide-treated rats, compared to 11 in the 12 untreated controls. Bromocriptine mesylate, at 10x the pergolide dose, was even less effective; one of 16 tumors regressed, 2 became static, and 8 new tumors appeared in the 16 rats. In contrast, 8 of 12 dimethylbenz(a)anthracene-induced tumors regressed during pergolide therapy, 2 became static, and there was only 1 new tumor among the 12 rats. Prolactin, 1 mg bid for 7 days by sc injection, was given to another eight rats bearing 11 N-nitrosomethylurea-induced tumors, commencing 7 days after hypophysectomy. Regression of five tumors borne by four rats was reversed but resumed when treatment was stopped. Regression of five tumors in the other four animals was arrested without regrowth; the sixth became impalpable. All of these six grew rapidly when growth hormone, 2 mg bid, was administered in addition to prolactin. (Author abstract) (21 Refs)

34. THE RELATIONSHIP BETWEEN DIETARY FAT AND HORMONES IN MAMMARY CARCINOGENESIS (MEETING ABSTRACT).

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International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Both epidemiologic findings and experimental data provide convincing evidence to support the concept that the etiology of cancer is multifactorial. In experimental mammary carcinogenesis, polypeptide and steroid hormones have been shown to be involved in the initiation and promotion phases of mammary tumor induction. Among the environmental factors suspected to play a role in mammary carcinogenes is, dietary fat correlates well with breast cancer incidence. This paper will present experimental data to demonstrate the co-carcinogenic effect of hormones in the induction of mammary cancer in the rat by polycyclic aromatic hydrocarbons. The experimental data will be compared with human epidemiologic findings. The relationship between dietary fat and mammary carcinogenesis in experimental models will be presented and, finally, the possible relationship between dietary fat and hormones will be discussed. (no Refs)

35. THE EFFECT OF INTERVAL BETWEEN NEUTRON RADIATION AND DIETHYLSTILBESTROL ON MAMMARY CARCINOGENESIS IN FEMALE ACI RATS (MEETING ABSTRACT).

Shellabarger CJ, Stone JP, Holtzman S
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International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Both radiation and diethylstilbestrol (DES) are carcinogens for the mammary gland of ACI female rats. When DES is given at about the same time as radiation, DES and radiation interact in a synergistic fashion particularly in regard to the number of mammary adenocarcinomas per rat. We have studied the effect of increasing the time interval between radiation and DES on the capacity of DES to enhance (promote?) radiation-induced mammary carcinogenesis. DES, in the form of a compressed pellet containing a mixture of cholesterol and DES, formulated to av 1.25 mg of DES per 100 g of body wt, was given to groups of approx 28 rats at either 2 days before, or 50, or 100, or 200 days after 0.064 Gray of 0.43 meV neutron radiation. At each time that DES was given to irradiated rats, DES was also given to non-irradiated rats. All rats were studied for 375 days after the date of the DES administration. When the total number of mammary adenocarcinomas was calculated as a percentage of 24 sites per rat at-risk, DES and radiation always produced a response that was larger than the sum of the responses of DES alone plus radiation alone. This result suggests that these two agents can interact in a synergistic fashion. The interaction between radiation and DES did not decline as the time interval between radiation and DES was lengthened. This result suggests that radiation-induced (initiated?) mammary carcinogenesis is not subject to repair since DES enhancement (promotion?) continues to be effective over long time intervals. (no Refs)

36. CHANGES IN ESTROGEN RECEPTOR LEVELS DURING DES-INDUCED HEPATOCARCINOGENESIS IN THE SYRIAN HAMSTER: A NEW TUMOR MODEL (MEETING ABSTRACT).

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Fifth International Symposium of the Journal of Steroid Biochemistry, July 13-15, 1981, Puerta Vallarta, Jalisco, Mexico. Journal of Steroid Biochemistry 80 pp., 1981.

A definite causal relationship exists between estrogens and liver tumors in women. At present there are no adequate estrogen inducible experimental liver tumor models available. The spontaneous liver tumor incidence in Syrian golden hamsters is

negligible and the incidence of hepatomas following continuous diethylstilbestrol (DES) or other estrogens, as in other rodents, has been reported to be low. Our present results indicate at least a 60% incidence in multifoci liver neoplasms in castrate male hamsters treated with DES for 8.0-mo and fed a diet containing 0.2% alpha-naphthoflavone (alpha-NF); an inhibitor of mixed function oxygenases. There is a nearly 3-fold elevation in specific estrogen binding in the livers of animals treated with DES for 2-to 3-mo compared to untreated hamsters and at least a 6-fold increase in liver estrogen receptor in hamsters treated with DES + alpha-NF. Sucrose gradient centrifugation analyses indicate either 8S or 8S + 4S binders in liver cytosols derived from these animals based on competition at 100-fold excess radioinert DES concentrations. Enhanced retention of estrogen receptor complex was observed in purified nuclei derived from hamsters treated with DES + alpha-NF compared to untreated controls. These findings may have an important role in liver tumorigenesis in the hamster. (no Refs)

37. ORAL CONTRACEPTIVE STEROIDS AS PROMOTERS AND COMPLETE CARCINOGENS FOR LIVER IN FEMALE SPRAGUE DAWLEY RATS (MEETING ABSTRACT).

Yager JD

New York University Medical School, New York, NY

International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Recent reports have described an increased incidence of adenomas and hepatocellular carcinomas in livers of women with a history of long-term oral contraceptive use. Evidence derived from human and experimental animal data suggests that oral contraceptive steroids may be liver tumor promoters. Studies being carried out in my laboratory were designed to determine whether two oral contraceptive steroids, mestranol and norethynodrel, can promote diethylnitrosamine (DEN)-initiated hepatocarcinogenesis. Studies have also been conducted to determine whether these agents exhibit any detectable genotoxic effects on liver cells which would indicate that they are capable of initiating hepatocarcinogenesis. In the studies designed to detect the promoting potential of these agents, female Sprague-Dawley rats were partially hepatectomized and treated with DEN 24 hr later to initiate hepatocarcinogenesis. Twenty-four hr after injection the animals were transferred to diet containing the agent to be tested. In two separate experiments, animals wer e killed after 4, 9 and 12 mo of feeding diets containing the oral contraceptive steroids. Both intact animals and hepatocytes in primary culture were employed in studies designed to detect the ability of the oral contraceptive steroids to cause genetic damage in liver cells. Genotoxicity was assessed by using techniques to detect DNA damage either directly or indirectly. The results from all of these studies indicate the following: 1) mestranol and norethynodrel can promote DEN-initiated hepatocarcinogenesis as indicated by increased numbers of gamma-glutamyl transpeptidase positive, putative preneoplastic lesions after 4 and 9 mo and possibly adenomas and carcinomas after 12 mo; 2) mestranol appears to cause alterations in DNA as detected using alkaline elution; however, this is not reflected by the occurrence of detectable levels of DNA repair. (1 Ref)

38. PROMOTING EFFECT OF TESTOSTERONE PROPRIONATE ON EXPERIMENTAL EXOCRINE PANCREATIC TUMORS BY 4-HYDROXYAMINOQUINOLINE 1-OXIDE IN RATS.

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Toxicol Lett; 9(4):349-354 1981

The promotion of 4-hydroxyaminoquinoline 1-oxide (HAQO) induced pancreatic tumors by androgenic hormone was tested in male and female rats. Three male (1m, 2m, and 3m) and three female groups (1f, 2f, and 3f) each consisting of 20 rats received 9 mg/kg iv injection of HAQO. Groups 1m and 1f received no further treatment. All other groups were castrated and subsequently given weekly sc injections of 1 mg testosterone propionate (groups 3m and 3f) or 0.1 ml olive oil (groups 2m and 2f). At 400 days the rats were autopsied and representative samples of pancreatic tumors were examined by electron microscopy. Eight exocrine adenomas of the pancreas developed in group 1m; six exocrine tumors developed in group 3m. One exocrine insuloma pancreatic tumor developed in group 1f and five were observed in group 3f. No exocrine adenomas of the pancreas developed in the control group or in groups 2m or 2f. Apparently testosterone can promote the induction of pancreatic tumors in rats by HAQO. (9 Refs)

MODIFICATION OF CARCINOGENESIS BY VIRUSES, BACTERIA OR IMMUNE SYSTEM COMPONENTS

39. CONVERSION OF HERPETIC LESIONS TO MALIGNANCY BY ULTRAVIOLET EXPOSURE AND PROMOTER APPLICATION.

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J Gen Virol; 55(part2):305-313 1981

Many lines of evidence exist associating herpes simplex virus (HSV) with the development of carcinoma, but much of this evidence in anecdotal or associative in nature and does not prove a cause and effect. The purpose of this research was to investigate the oncogenic potential of HSV Type 2 (HSV-2) in vivo. A mouse model for lip carcinogenesis was designed to combine HSV-2 infection, UV exposure and tetradecanoylphorbol-acetate (TPA) application. HSV-2 inoculation on to abraded mouse lips was capable of causing vesicular ulcerative lesions which healed completely after 10 to 14 days. UV irradiation of the HSV lesion site daily for 6 min at 42 ergs/mm2/s on days 3 to 6 post-infection caused hyperkeratosis, acanthosis and dysplasia to develop in several lips; while the same UV exposure by itself failed to alter the histologic appearance. The addition of repeated TPA application to the HSV + UV regimen promoted tumor emergence. Thirty-two of 156 Balb/c mice developed tumors. Although the majority were papillomas, six were squamous cell carcinomas. These tumor-bearing mice had increased HSV-specific antibody titers. HSV antigens were shown to be present in outgrowths from explanted tumors as well as in tumor biopsies by immunoperoxidase staining with HSV-specific antisera. It is suggested that the in vivo UV-irradiated HSV acted as an inducer and TPA as the pro-

moter, analogous to the classical two-stage carcinogenesis model. (Author abstract) (29 Refs)

40. EFFECT OF HERPES INFECTION ON INDUCTION OF CERVICAL CANCER BY METHYLCHOLANTHRENE IN MICE (MEETING ABSTRACT).

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Department of Obstetrics and Gynaecology, Hyogo Medical College, Nishinomiya, Japan

Obstetrics and Gynaecology: 8th Asian Congress, October 25-31, 1981, Melbourne, Australia. Asia and Oceania Federation of Obstetricians and Gynaecologists 352 pp., 1981.

It is unknown whether herpes simplex virus type 2 (HSV-2) is one of the possible etiologic agents of human cervical cancer or not. The present study was performed to evaluate any possible carcinogenic activity of HSV-2 in the genital tract of the female mouse. The 'string method' of methylcholanthrene (MC) was used to induce carcinoma of the uterine cervix in mice. Two kinds of experiments were designed as follows: (1) Impregnation of MC threads was first carried out, and 7 wk later these were removed and half of the mice were infected with HSV-2 in the genital tract, while the other half were not. One, 2 and 3 mo later, several mice from both groups were sacrificed and the histological changes in the squamous and columnar epithelium were examined. A synergistic effect of MC and HSV-2 on the columnar areas was not observed, whereas this effect was clearly demonstrated on the squamous areas, especially in the specimens prepared from the mice at 3 mo after HSV infection. (2) Mice were first infected and 10 days later MC treatment was carried out. Three experimental groups of HSV(+)MC(+), HSV(+)MC(-), and HSV(-)MC(+) treated mice studied as controls. Four mo after MC treatment, all mice were sacrificed and examined. In this experiment, the appearance of atypia III (corresponding to carcinoma-in situ in the human) and invasive lesions of the cervix were frequently detected in the group of HSV(+)MC(+). From these investigations, it is postulated that herpetic infection may enhance induction of cervical cancer. (no Refs)

41. POSSIBLE ROLE OF ENDOGENOUS MMTV VIRUS IN CHEMICAL MAMMARY GLAND CARCINOGENESIS IN MICE.

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Biull Eksp Biol Med; 91(9):339-342 1981

The effect of immunization with inactivated endogenous MMTV virus on the yield of dimethylbenz(a)anthracene (DMBA)-induced mammary gland tumors was studied in BALB/c mice free of exogenous virus. The animals were first administered DMBA (1 mg/day, 1.5 mo, po); then, 1 wk later, they were immunized with formaldehyde-treated suspension of MMTV. Control mice were immunized with Moloney leukemia virus (MuLV). Mammary gland neoplasms were detected in 21% of the mice immunized with MMTV, compared with 39% of MuLV-immunized mice and 40% of nonimmunized mice. The av latent period of tumor development in the MMTV-immunized mice was 119 days, compared with 88 days in the MuLV-immunized mice and 82 days in nonimmunized mice. Indirect immunofluorescence analysis showed expression of gp52 and p27 viral antigens in tumor tissues from both the immunized and the control mice. (11 Refs) (In RUS)

42. INFLUENCE OF SERUM THYMIC FACTOR (F.T.S.) ON RADIATION-INDUCED LEUKAEMOGENESIS IN THYMECTOMIZED AKR MICE (MEETING ABSTRACT).

Legrand E, Daculsi R, Bach JF, Duplan JF

No affiliation given

Exp Hematol; 9(Suppl9):67 1981

The influence of serum thymic factor (FTS) on extra-thymic leukemogenesis induced in thymectomized AKR mice exposed to fractionated sub-lethal irradiation was studied. Thirty day-old thymectomized mice were submitted to 4 weekly doses (1.75 Gray) and thereafter treated with FTS (1 ng) for 9 days. Two groups were restored with either bone marrow (BM) or spleen cells prior to FTS treatment. In another group, mice were treated with FTS (12 ng) for one mo after thymectomy and prior to irradiation. Results indicated that primarily irradiation and FTS, and to lesser extents, restoration and age of the mice at the time of their first radiation exposure influenced leukemogenesis. Irradiation increased the spontaneous low incidence of extra-thymic leukemia up to 50%. Although indication about the expression of endogenous retroviruses in thymectomized AKR is still missing, the possible expression of leukemogenic recombinants either identical to or different from AKR MCF viruses might explain the enhancing effect of radiation in leukemogenesis. Mice developed two types of leukemias: 'null' leukemias whose cells did not bear any detectable theta antigen or surface immunoglobulin and B leukemias. Among the null leukemias, two kinds coul d be distinguished: 'early' ones which were observed before 450 days, and in which BM and spleen were similarly involved; 'late' ones which displayed the same characteristics as B leukemias ie delayed appearance and splenic origin. Although FTS did not modify the overall frequency of leukemias, it increased significantly the incidence of the 'early' null ones. It had no effect on the frequency nor the latency of late null and B leukemias. Any population of theta negative T cells sensitive to FTS could be an acceptable candidate for 'early' null leukemogenesis. (no Refs)

OTHER STUDIES OF THE MODIFICATION OF CARCINOGENESIS

43. EFFECT OF AGE AT START OF DIETHYLSTILBESTROL (DES) TREATMENT ON MAMMARY TUMOR INDUCTION IN C3H MICE (MEETING ABSTRACT).

Greenman DL, Cameron A, Highman B, Frith CH, Norvell MJ

National Center of Toxicology Research, Jefferson, AR

Toxicologist; 1(1):155 1981

To determine the effect of age at the start of DES administration, C3H/HeN female mice with a high (MTV+) and low (MTV-) titer of murine mammary tumor virus were continuously fed a diet containing 640 ppb DES. MTV+ mice were started on DES at ages 21, 35, 49, or 77 days (d) and MTV- mice at 21, 35, 49, or 63 d. Mammary tumors were detected by palpation and mice were removed from experiment when tumor reached a diameter of 1 cm. Time-to-tumor data are based on time of removal with a histologically verified mammary tumor. DES induced only mammary tumors in MTV+ mice. In the longer-lived MTV- females, DES induced mammary tumors and a low frequency of pituitary adenomas, uterine adenocarcinomas and mesotheliomas. The DES starting age

affected only mammary tumor induction. In MTV+ mice, the percentages of the starting populations that developed mammary tumors (frequency) were 86% for controls, 88% for mice started at 49 or 77 d and 98% for mice started at 21 or 35 d. The times till half of the starting populations had tumors (t50) were 265 d for controls, 190 d for the 49 and 77 d mice, and 160 d for mice started at 21 or 35 d. In MTV- females, frequencies were 2% for controls and 50%, 80%, or 88% for mice started at 49 or 63 d, 35 d, and 21 d respectively. For these latter 3 groups, t50s were 850, 500, and 385 d, respectively. Age at the start of treatment strongly influenced the effect of DES on mammary tumor frequency and time-to-tumor in C3H (MTV-) but had less effect in MTV+ mice. These findings point out the important role age at the initiation of treatment may have in evaluating the potential toxicity of a test compound. (no Refs)

44. MODIFYING FACTORS IN PANCREATIC CARCINOGENESIS IN THE SYRIAN HAMSTER MODEL. I. THE EFFECT OF DUCT LIGATION AND PARTIAL PANCREATECTOMY (MEETING ABSTRACT).

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Newsletter Natl Pancreas Cancer Project; VI(2):47 1981

By examining the effect of pancreatic duct ligation and partial pancreatectomy on the overall pancreatic carcinogenicity of a single injection of N-nitrosobis(2-oxopropyl)amine (BOP), it was found that the incidence and the multiplicity of tumors were significantly decreased after both types of surgery when BOP was given immediately after the wound closure, but not when BOP was given later, ie after 3 days or 1 wk. For example, 62% of all hamsters treated with BOP one wk after partial pancreatectomy developed tumors, whereas only 8% of those receiving the same dose immediately after surgery showed the equivalent neoplasms. In comparison, a 60% tumor incidence occurred in hamsters not operated upon or which received the carcinogen later than 3 days after the surgery. It is interesting that a similar pattern was also observed in sham-operated BOP-treated hamsters. The pattern of benign and malignant tumors induced by each procedure will be presented, and the possible reasons for inhibition of tumor development by surgery will be discussed. (no Refs)

45. TISSUE DAMAGE AND NUTRITIONAL FACTORS IN EXPERIMENTAL RESPIRATORY TRACT (CO-) CARCINOGENESIS (MEETING ABSTRACT).

Kroes R, Reuzel PG, Feron VJ, Spit BJ, Beems RB
Institute CIVO-Toxicology and Nutrition TNA, The Netherlands
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Co-factors involved in respiratory tract carcinogenesis are studied in Syrian golden hamsters using benzo(a)pyrene as the carcinogenic agent. These factors include severe tissue damage induced by electro-coagulation, glass fibers administered by intratracheal instillation, acetaldehyde as irritant vapor, food restriction, and nutrients such as vitamin A and saturated and unsaturated fats. A combined exposure to four different major gaseous cigarette smoke components viz methyl nitrite and isoprene and one solid cigarette smoke component, nor-harman are examined in short- and long-term inhalation studies. An interesting finding was the carcinogenicity of acetaldehyde, of which the possible mechanism is briefly discussed. Another conspicuous observation was the substantial increase in number and size of lipid droplets in alveolar macrophages of hamsters fed a high vitamin A diet. (no Refs)

46. EFFECTS OF RAT URINE FRACTIONATED BY MOLECULAR WEIGHT ON URINARY BLADDER CARCINOGENESIS.

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Cancer Res; 42(1):15-18 1982

Experimental evidence suggests that rat urine plays a dual role in urinary bladder carcinogenesis, as a carrier of carcinogen(s) and an enhancer (or promoter) of carcinogenesis in carcinogen-initiated cells. The present experiment was conducted to determine whether -tumor-enhancing activity exhibited by the whole urine resides in a specific fraction(s) when separated by mol wt. Normal rat urine after preliminary filtration to remove gross debris was filtered through Amicon Diaflo membranes to obtain two types of filtrate, one at an exclusion level of mol wt 1,000 and the second at an exclusion level of mol wt 50,000. These filtrates were tested for tumor-enhancing activity in the heterotopically transplanted rat urinary bladders (HTBs) removed from rats pretreated with the carcinogen N-butyl-N-(4-hydroxybutyl)nitrosamine in drinking water for 4 or 10 wk. The incidences of cancer in HTBs receiving repeated instillations of the filtrate at mol wt 50,000 did not differ significantly from those of the HTBs receiving whole urine but were significantly higher than those of the HTBs receiving the filtrate at mol wt 1,000. In the HTBs, which had been exposed to the carcinogen for a longer period of time (10 wk), the filtrate at mol wt 1,000, enhanced the bladder tumorigenesis over that of the osmolality control. The results indicate that there may be two classes of tumor-enhancing activity: the first and major one being in the fraction above mol wt 1,000; and a second one being below mol wt 1,000. the latter fraction appears to exert its effects only on the cells which are in an advanced stage of carcinogenesis. (Author abstract) (10 Refs)

STUDIES OF TUMOR PROMOTION OR COCARCINOGENESIS IN MOUSE SKIN

47. PROMOTION OF CARCINOMAS BY REPEATED ABRASION IN INITIATED SKIN OF MICE.

Argyris TS, Slaga TJ
Dept. Pathology, Upstate Medical Center, Syracuse, NY, 13210
Cancer Res; 41(12):5193-5195 1981

Repeated abrasion of the skin of Sencar mice initiated with 100 nmol of dimethylbenzanthracene resulted in the appearance of carcinomas in addition to papillomas. These results strongly support the argument that repeated epidermal regeneration is a sufficient stimulus for the promotion of both benign and malignant neoplasms in the skin of mice. (Author abstract) (5 Refs)

48. THE EFFECT OF CAFFEINE ON TWO-STAGE SKIN CARCINOGENESIS AND ON COMPLETE SYSTEMIC CARCINOGENESIS.

Armuth V, Berenblum I
Experimental Biology Unit, Weizmann Inst. Science, 76100 Rehovot, Israel
Carcinogenesis; 2(10):977-979 1981

The effect of a single large dose of caffeine (100 ug/g, sc) on skin and lung tumorigenesis in female ICR mice, using urethan as an initiator and anthralin as a promoter, was investigated. Topical treatment with urethan and anthranil resulted in a 37% (11/30) incidence of papilloma-bearing mice, with an av of 1.27 papillomas/mouse. Caffeine significantly augmented tumor incidence (to 60%) when injected 6 hr before initiation. Caffeine produced a smaller increase in the incidence of papillomas when administered 9 hr before initiation, whereas it was associated with an insignificant decrease when administered 6 hr after initiation. Induction of lung adenomas by urethan was unaffected by caffeine administration. The results suggest that timing of a large single dose of caffeine might determine the direction of its gene-modulating effect. (16 Refs)

49. CELL POPULATION KINETICS IN HAIRLESS MOUSE EPIDERMIS FOLLOWING A SINGLE TOPICAL APPLICATIONS OF 12-O-TETRADECANOYLPHORBOL-13-ACETATE I.

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Carcinogenesis; 2(10):999-1006 1981

Cell population kinetics of hairless-mouse (Oslo strain) epidermis following a single, topical application of 17 nanomoles of 12-O-tetradecanoylphorbol-13-acetate (TPA) were investigated by flow cytometry and by measuring thymidine incorporation into DNA, mitotic index, and colcemid-arrested metaphase rates. The early epidermal cell kinetic reaction to TPA was divided into two periods: period 1 (0-12 hr), characterized mainly by a block in cell proliferation, and period 2 (12-96 hr), characterized mainly by rapid proliferation leading to hyperplasia. Thus, TPA treatment leads to an immediate block of cells in S-phase and mitosis, thereby triggering the cells to proceed, partly synchronized, through several cycles of cell division. The fact that hyperplastic epidermis is composed of a higher proportion of young, immature cells, which are functionally and morphologically different from mature cells, may account for some biochemical changes occurring after TPA application. (48 Refs)

50. EFFECTS OF THE PHORBOL ESTER 4-O-METHYL-12-O-TETRADECANOYLPHORBOL-13-ACETATE ON MOUSE SKIN IN VIVO: EVIDENCE FOR ITS USELESSNESS AS A NEGATIVE CONTROL COMPOUND IN STUDIES ON THE BIOLOGICAL EFFECTS OF PHORBOL ESTER TUMOR PROMOTERS.

Furstenberger G, Richter H, Argyris TS, Marks F
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Cancer Res; 42(1):342-348 1982

Compared to 12-O-tetradecanoylphorbol-13-acetate (TPA), the phorbol ester 4-0-methyl-12-0-tetradecanoylphorbol-13-acetate (4-O-methyl-TPA) is only a weak skin irritant and tumor promoter. When topically applied to mouse skin, 400 nmol 4-O-methyl-TPA induce hyperproliferation of epidermis in vivo to approx the same extent as do 10 nmol TPA. However, in contrast to TPA, 4-O-methyl-TPA-induced proliferation is not followed by sustained epidermal hyperplasia. In addition, the methyl ether of TPA does not cause early prostaglandin accumulation, and its hyperproliferative effect is insensitive to indomethacin inhibition. Contrary to the action of TPA, 4-O-methyl-TPA induces neither an early increase in the rate of phospholipid turnover nor an early increase in ornithine decarboxylase activity or polyamine accumulation in epidermis and does not desensitize epidermis to the effects of beta-adrenergic agonists and epidermal G chalone. Finally, 4-O-methyl-TPA is only a weak stimulator of epidermal cyclic AMP phosphodiesterase activity. Consequently, it is concluded that the mechanism of action of 4-O-methyl-TPA as a skin mitogen is different from that of TPA. Whereas TPA evokes prostaglandin-dependent and chalone-insensitive hyperplastic development of epidermis (hyperplastic transformation), ie, probably a relapse to the neonatal state, 4-O-methyl-TPA apparently stimulates nothing but normal everyday tissue regeneration. In this respect, treatment with 4-O-methyl-TPA resembles a non-damaging stimulus of epidermal cell proliferation (observed, for example, with skin massage), whereas TPA evokes a response which is characteristic for epidermal injury. Considering these fundamental differences in biological action between TPA and its methyl ether, 4-O-methyl-TPA is concluded to be an unsuitable negative control compound for studies on the biological effects of phorbol ester tumor promoters. (Author abstract) (41 Refs)

51. POTENT ENVIRONMENTAL TUMOR PROMOTERS FOUND IN STREPTOMYCES AND BLUE-GREEN ALGA (MEETING ABSTRACT).

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International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

It is well known that tumor promoters induce ornithine decarboxylase (ODC) activity in mouse skin and that this induction can be inhibited by the application of 13-cis-retinoic acid. These two properties of tumor promoters were utilized for screening new tumor promoters in our environment. Two new classes of tumor promoters are presented: 1) Indole alkaloid (teleocidin and lyngbyatoxin); and 2) Polyacetate (aplysiatoxin and debromoaplysiatoxin). Teleocidin from Streptomyces and lyngbyatoxin, from the blue-green alga, Lyngbya majuscula, were able to induce ODC activity in mouse skin and showed various biological activities similar to those of tetradecanoyl phorbol acetate (TPA). Teleocidin and lyngbyatoxin are indole alkaloids. Their tumor promoting activities became apparent in the mouse skin through a two-stage carcinogenicity test. The tumor incidence of the group treated with dimethylbenzanthracene (DMBA) plus teleocidin was 100% at wk 30, which was similar to that of the group given DMBA and TPA. The in vivo carcinogenicity test with lyngbyatoxin is still underway. The tumor incidence of the group treated with DMBA plus lyngbyatoxin is 80% at wk 21. A second new class of tumor promoter is polyacetate. Aplysiatoxin and debromoplysiatoxin were isolated from another variety of blue-green alga. Aplysiatoxin and debromoaplysiatoxin induced ODC to the same degree of potency. However, aplysiatoxin induced various membrane effects, such as adhesion of cells and turnover of phospholipid with a similar concentration of TPA, teleocidin and lyngbyatoxin. On the other hand, debromoaplysiatoxin required an amount almost 100 x greater to achieve the same effects. (no Refs)

CELL CULTURE STUDIES OF MECHANISMS OF MODIFICATION

52. TUMOR PROMOTION STUDIES IN RAT TRACHEAL EPITHELIUM (MEETING ABSTRACT).

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National Institute of Environmental Health Sciences, Research Triangle Park, NC
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Tracheal epithelium of the Fisher 344 rat is histologically very similar to that of the human bronchus. Also, carcinomas of tracheal origin in F-344 rats are similar in morphology to human bronchogenic carcinomas. Two model systems exist to study tumor promotion in rat tracheal epithelium. The first is a heterotopic tracheal transplant system in which rat tracheas are implanted sc on the backs of isogenic recipients. The epithelium was then topically exposed to pellets containing 7,12-dimethyl-benz(a)anthracene, DMBA, used as the initiating agent, followed by pellets containing the phorbol ester 12-O-tetradecanoylphorbol-13-acetate, TPA, the promoting agent. After 98 wk, 3-4 fold increase in the percentage of tracheas having malignant tumors was seen in tracheal transplants receiving both DMBA and TPA compared to DMBA alone. Exposure of the tracheal grafts to TPA alone resulted in epithelial hyperplasia and inflammation, but no dysplastic lesions. The second system is an organ culture-cell culture system in which small pieces of trachea are grown in organ culture, then epithelial cells are grown from these pieces as primary cell cultures. The organ cultures were exposed to the direct alkylating agent, N-methyl-N'-nitro-N-nitrosoguanidine, MNNG, used as the initiator, then multiple short exposures to TPA are used to promote. Primary cell cultures and cell lines were then established from these explants. After 52 wk, a five-fold increase in the percentage of explants producing tumorigenic cell lines was observed when MNNG + TPA exposed explants were compared to MNNG exposed explants. Tracheal explants exposed to TPA alone produced many cell lines but none tested were tumorigenic. These two systems provide a means to study tumor promotion in respiratory epithelium. The evidence more importantly suggests that airborne promoting substances may play a key role in the development of bronchogenic carcinoma. (no Refs)

53. DISSOCIATION OF MITOGENESIS AND LATE-STAGE PROMOTION OF TUMOR CELL PHENOTYPE BY PHORBOL ESTERS: MITOGEN-RESISTANT VARIANTS ARE SENSITIVE TO PROMOTION.

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Cell Biology Section, Lab. Viral Carcinogenesis, NCI, Frederick, MD, 21701
Proc Natl Acad Sci USA; 78(11,part2):6912-6916 1981

The JB-6 mouse epidermal cell line has been used as a model system for studying the mechanism of late-stage promoter-dependent preneoplastic progression. The studies reported here are concerned with determining whether there is a requirement for mitogenic stimulation in promotion of anchorage independence and tumorigenicity in JB-6 cells. Such a requirement would predict that variants selected for 12-O-tetradecanoylphorbol 13-acetate (TPA) mitogen resistance would also be promotion resistant. Promotion-responsive cell lines have been selected for resistance to TPA-induced mitogenic stimulation at plateau density by cotreatment with colchicine and removal of mitogen-responsive colchicine-detached cells. The selected TPA-resistant population of cells showed a mitogenic response that was diminished by a factor of four but showed no diminution in the promotion-of-anchorage-independence response to TPA. Mitogen-resistant clonal lines derived from the selected population fell into three phenotypic classes when assayed in soft agar: (i) anchorage-independent transformants; (ii) variants resistant to promotion of anchorage independence by TPA; and (iii) variants sensitive to promotion by TPA. The existence of the latter class (ie, the mitogen-resistant promotable variants) indicates a lack of obligatory causal relationship between TPA-induced mitogenesis and late-stage promotion and, thereby, suggests that the two events can be dissociated. (Author abstract) (22 Refs)

54. PHORBOL ESTER-INDUCED ANCHORAGE INDEPENDENCE AND ITS ANTAGONISM BY RETINOIC ACID CORRELATES WITH ALTERED EXPRESSION OF SPECIFIC GLYCOPROTEINS.

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Lab. Viral Carcinogenesis, NCI, Frederick, MD, 21701
Carcinogenesis; 2(10):951-958 1981

Biochemical studies in JB-6 mouse epidermal cells were carried out to determine whether specific changes in glycoprotein synthesis might be targets for tumor-promoting action of phorbol esters and for anti-promoting action of retinoids. Sodium dodecylsulfate-polyacrylamide gel electrophoresis profiles of cells treated with 12-O-tetradecanoyl-phorbol-13-acetate (TPA) at concentrations inducing anchorage independence in JB-6 cells (1-100 nanog/ml) showed substantial decreases in mannose, fucose, glucosamine, and galactose incorporation into glycoconjugates of approx 180,000 (gp 180), 150,000 (gp 150), and 220,000 (gp 220) daltons mol wt. Glycoprotein labeling was unaffected by TPA at 0.1 nanog/ml, a concentration which does not induce anchorage independence. Two TPA analogues, phorbol didecanoate and phorbol dibenzoate, reduced labeled mannose incorporation into the three glycoproteins, whereas phorbol and phorbol diacetate, which do not promote anchorage independence, had no effect. Retinoic acid (10(-6) M), a potent inhibitor of TPA-induced anchorage independence in JB-6 cells, enhanced mannose and leucine labeling of gp180 and gp150 and antagonized the TPA effect, suggesting that decreased gp180 and gp150 synthesis could be required in late-stage promotion. (22 Refs)

55. REGULATION OF GENE EXPRESSION BY TUMOR PROMOTERS. III. COMPLEMENTATION OF THE DEVELOPMENTAL PROGRAM IN MYELOID LEUKEMIC CELLS BY REGULATING MRNA PRODUCTION AND MRNA TRANSLATION.

Hoffman-Liebermann B, Liebermann D, Sachs L
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Int J Cancer; 28(5):615-620 1981

Regulation of gene expression has been analyzed in different clones of mouse myeloid leukemic cells treated with the tumor promoter 12-O-tetradecanoyl-phorbol-13-acetate (TPA), the macrophage- and granulocyte-inducing protein MGI, and combined treatment with TPA and MGI. Two-dimensional gel electrophoresis was used to measure changes in the rate of synthesis of specific proteins and in the amount of corresponding translatable mRNAs assayed in the reticulocyte cell-free translation system. TPA induced different subsets of differentiation-associated protein changes in the different clones and the degree of response to TPA was not necessarily related to the degree of response to MGI. It is shown that TPA can induce

protein changes either by inducing the synthesis of new mRNA, by increasing or decreasing the amount of pre-existing mRNA, or by modulating the translation of a constant amount of mRNA. Combined treatment with TPA and MGI resulted in an enhancement of protein changes induced by MGI or TPA alone and induced differentiation-associated protein changes not induced by either compound separately in differentiation-defective clones. This complementation of gene expression appeared to be due to each compound inducing functions not induced by the other, so that the combined treatment resulted in new gene expression. Complementation also occurred at the level both of mRNA production and of mRNA translation. It is suggested that the ability of TPA to regulate gene expression at the level of mRNA production and mRNA translation and to complement changes in gene expression induced by other compounds such as MGI are important functions for its role as a tumor promoter. (Author abstract) (34 Refs)

56. THE INDUCTION OF ORNITHINE DECARBOXYLASE BY TUMOR PROMOTING PHORBOL ESTER ANALOGUES IN REUBER H35 HEPATOMA CELLS.

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Life Sci; 29(18):1855-1863 1981

The induction of ornithine decarboxylase activity was studied in a rat hepatoma cell line (Reuber H35) incubated with a group of structurally-related phorbol ester analogues. A single application of 1.6 uM of tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) to H35 cells caused a dramatic increase in the activity of ornithine decarboxylase. The stimulation of the enzyme activity was rapid but transient, peaking at 4 to 5 hr with a value which was 116-fold greater than control and then declining to the basal level after 8 hr. In addition, the increase in ODC activity was dependent upon the concentration of TPA added to the culture medium and the EC50 was estimated to be about 2.63 x 10(-7) M. Our studies of the effect of various phorbol ester analogues on the H35 ODC activity indicated an apparent correlation between the ability of phorbol ester derivatives to induce ODC activity in the H35 cells and their activity to promote papilloma formation in the mouse skin in that the various derivatives possessed the following relative abilities to increase ODC activity: TPA greater than PDB greater than PDA greater than 4 alpha-P greater than 4 alpha-PDD. Concurrent addition of either actinomycin D or cycloheximide abolished the increase in ODC activity after TPA treatment. Changes of intracellular concentrations of polyamines, particularly putrescine, were in good agreement with the increase in ODC activity in response to TPA: a 10-fold increase in putrescine over the control level was observed at 6 hr. Our data suggest that cultured Reuber H35 hepatoma cells exhibit a marked and specific response to the phorbol ester tumor promoters and may be of great value in studying the biochemical mechanism of ODC induction by these agents. (Author abstract) (33 Refs)

57. TUMOR PROMOTERS INDUCE THE SYNTHESIS OF A SECRETED GLYCOPROTEIN IN MOUSE SKIN AND CULTURED PRIMARY MOUSE EPIDERMAL CELLS.

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Carcinogenesis; 2(10):971-976 1981

Effects of tumor promoters and anti-promoters on synthesis and secretion of a 35,000 dalton transformation-dependent secreted glycoprotein (major excreted protein, MEP) by primary mouse epidermal cells were investigated. 12-O-Tetradecanoylphorbol-13-acetate (TPA) increased synthesis and secretion of MEP, an effect that was maximal at 6 hr. This time course is consistent with an effect of TPA on transcription of MEP messenger RNA. The induction of MEP synthesis was very sensitive to TPA, with half-maximal stimulation (at 3 nanog/ml or less). TPA also induced MEP synthesis in mouse skin in situ. The anti-promoters lidocaine and retinoic acid had no effect on basal MEP synthesis or secretion, or on TPA stimulation. Fluocinolone acetonide decreased basal levels of MEP synthesis without blocking TPA-induced MEP synthesis. The data suggest that the effects of the three anti-promoters are not mediated via an alt eration in MEP synthesis or secretion and that an increase in MEP synthesis per se is not sufficient for promotion. (33 Refs)

58. INHIBITION OF METABOLIC COOPERATION AND CELL GROWTH BY PHORBOL ESTERS (MEETING ABSTRACT).

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Cell Biol Int Rep; 5(SupplA) 1981

A strong correlation exists between the ability of phorbol esters to promote tumors in mouse skin two-stage carcinogenesis assays and their ability to block metabolic cooperation between cells. This poster details the interactions between TPA (12-O-tetradecanoyl-phorbol-13-acetate), PDB (phorbol-12,13 di-butyrate) and 4-O-methyl tetradecanoyl-phorbol acetate and cells of an SV-40 transformed human keratinocyte line. Using 10(-8) -10-7M 3H-PDB specific binding to the keratinocytes (ie displaced by 1000 fold excess of cold PDB) has been demonstrated. Overnight incubation of keratinocytes in 10-7M PDB or TPA but not 4-O-MeTPA (a very weak promoter) results in loss of their ability to transfer 3H-hypoxanthine to recipient keratinocytes. Further incubation (up to 10 days) results in a specific, reversible inhibition of keratinocyte growth. While in the presence of TPA or PDB, the cells multiply but the number of cells per culture is much lower compared with vehicle or 4-O-MeTPA treated controls. Tumor promoters are known to induce hyperplasia in mouse skin. We have shown that TPA has the reverse effects on a human epidermal keratinocyte line. There are many possible explanations of this apparent contrast. The link between inhibition of junctional communication and subsequent inhibition of growth is currently under investigation. (1 Ref)

59. SPECIFIC BINDING OF PHORBOL ESTERS BY PANCREATIC ACINI AND ACINAR CARCINOMA CELLS (MEETING ABSTRACT).

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Newsletter Natl Pancreas Cancer Project; VI(2):24 1981

The phorbol ester 12-O-tetradecanoyl-phorbol-13-acetate (TPA) triggers the discharge of secretory protein from pancreatic acini in an energy-dependent manner, without stimulating Ca++ efflux or elevating intracellular levels of cyclic nucleotides. Since receptors for TPA have been identified on other cell types, a search for specific binding to guinea pig pancreatic acini was carried out using the radiolabeled phorbol derivative (20-3H)-phorbol-12,13-dibutyrate (3H-PDBu). PDBu also stimulates discharge, with an optimally stimulating dose (3x10(-6) M) 10-fold higher than that required for TPA. 3H-PDBu binding was found to be specific in that up to 70% of the cell-

associated radioactivity was inhibitable by excess unlabeled PDBu. Specific binding reached a max in either 5 min at 20 C or 2 hr at 4 C, and Scatchard analysis under the two conditions gave equivalent results. PDBu bound to 8.0 x 10(4) sites/pgm DNA with a KD of 1.1 x 10(-7) M. The PDBu binding sites are apparently of two types, however, since TPA and other phorbol esters with secretagogue activity compete for only 30-40% of the available PDBu receptors. Phorbol derivatives that do not stimulate discharge do not inhibit 3H-PDBu binding, and binding is not affected by caerulein, carbamylcholine, secretin or vasoactive intestinal peptide. Phorbol ester receptors with similar characteristics were also found on normal rat acini and on cells from a rat acinar carcinoma. These findings are consistent with the hypothesis that phorbol esters trigger pancreatic discharge through interaction with specific cellular receptors. (no Refs)

60. PHORBOL ESTERS PARALLEL EFFECTS ON TUMOR PROMOTION, INSULIN RELEASE AND CALCIUM IONOPHORESIS.

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Cancer Lett; 14(2):109-114 1981

Mechanisms by which the tumor promoters 12-O-tetradecanoyl-phorbol-13-acetate (TPA) and phorbol 12,13-didecanoate (PDD) may exert their early (insulin release) and late (tumor promotion) biological effects were investigated. In the presence of 5.6 mM glucose, TPA and PDD stimulated insulin release from isolated rat pancreatic islets. 4alpha-PDD and phorbol, non-tumor promoters, failed to exert similar effects when tested at the same concentration (0.2 uM). When incubated at 37 C, liposomes containing a phorbol ester but no calcium ionophore (A23187) released 45Ca at the same rate as control liposomes. In the presence of A23187, both TPA and PDD increased the rate of 45Ca efflux from the liposomes, whereas 4alpha-PDD did not. Increases in A23187-mediated calcium transport attributable to TPA and PDD were 24.4% and 20.3%, respectively, above control values. Phorbol decreased the A23187-mediated efflux of 45Ca. (14 Refs)

61. MEMBRANE ALTERATIONS IN FUSING AND PHORBOL ESTER-TREATED MYOGENIC CELLS.

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Diss Abstr Int [B]; 42(4):1431-B 1981

Cultured chick embryo myogenic cells differentiate and fuse to form multinucleated myotubes which become striated and acquire the potential to undergo Spontaneous Contractions. The diterpene tumor promoter, phorbol-12-myristate 13-acetate (PMA) inhibits myoblast fusion. The most rapid effects of this lipophilic compound occur in plasma membrane-associated processes, such as ion transport and cyclic nucleotide generation. Changes in specific membrane proteins have also been reported to occur in PMA-treated myogenic cells. In addition to the reported alterations in the levels of membrane proteins of known function it was possible that PMA extensively altered the composition and metabolism of other plasma membrane proteins whose functions are unknown. This hypothesis was tested using radiolabeled leucine and mannosamine precursors and electrophoretic analysis of membrane proteins on polyacrylamide gels. By 8 hr incubation PMA altered plasma membrane protein and sialoglycoprotein composition. Stimulation of diacylglycerol levels (2-fold) and stimulation of the rate of label incorporated into phosphatidic acid (2-fold), phosphatidylinositol (3-fold) and phosphatidylcholine (2-fold) were observed within 15-30 min of treatment with PMA. The increase in each of these lipids was shown to arise by synthesis from pre-existing lipids rather than by de novo synthesis. Using a double-label turnover technique and fatty acid analysis, it was shown that phosphatidylcholine is the most probable precursor of the PMA-induced diacylglycerol fraction. Subcellular fractionation of the PMA-stimulated cells suggested that the diacylglycerol was generated in the plasma membrane. Possible models for the mechanisms of PMA-dependent alterations in lipid metabolism and myoblast fusion are discussed. (no Refs)

62. MODULATION OF HUMAN T-CELL DIFFERENTIATION MARKERS BY 12-O-TETRADECANOYLPHORBOL-13-ACETATE.

Nagasawa K, Chechik BE, Gelfand EW, Sengupta S, Letarte M, Mak TW
Ontario Cancer Inst., Toronto, Ontario, Canada
Thymus; 3(4/5):307-318 1981

Extent and sequence of changes in level of seven differentiation markers observed in the human leukemia T-cell line MOLT-3 after incubation with 12-O-tetradecanoylphorbol-13-acetate (TPA) were investigated. Terminal deoxynucleotidyl transferase (TdT) activity decreased rapidly after induction with 1.6 x 10(-8) M TPA. The decrease was not simply a loss of enzyme activity, because the percentage of cells containing TdT measured by single-cell immunofluorescence decreased concomitantly. TPA also induced a rapid, irreversible loss of spontaneous proliferative capacity in the cells. Approx 1 day after the addition of TPA, a linear increase in E-rosette-positive (E+) cells was observed. E+ cells increased to approx 50% of the total between days 3 and 4. TPA also caused a gradual decrease in adenosine deaminase (ADA) activity and HThy-L/ADA (human thymus-leukemia-associated antigen, a low mol wt form of ADA) to approx 30-50% of control values. TPA did not induce any significant changes in ecto-5'-nucleotidase activities, in the proliferative response to phytohemagglutinin, or in the expression of Ia-like antigens. Time kinetics of the changes suggest that the sequence of events induced by TPA is loss of TdT activity, loss of proliferative activity and ability to form E-rosettes, and a decrease in ADA (HThy-L/ADA). This sequence appears to follow that proposed for prethymic precursor T-cell differentiation after activation with thymic epithelium. (35 Refs)

63. TUMOR PROMOTING PHORBOL ESTERS INHIBIT BINDING OF COLONY STIMULATING FACTOR TO B ONE MARROW CELLS (MEETING ABSTRACT).

Stuart RK, Sensenbrenner LL, Waheed A, Camaratti C, Shadduck RK
Johns Hopkins Oncology Center, Baltimore, MD, 21205
Exp Hematol; 9(Suppl9):133 1981

Tumor promoting phorbol esters, such as 12-O-tetradecanoyl-phorbol-13-acetate (TPA) stimulate colony formation by murine granulocyte-macrophage progenitors (GM-CFC) in semisolid medium cultures that do not contain added colony stimulating factor (CSF). The active phorbol esters stimulate colony formation over a wide concentration range while the parent compound, phorbol, and its non-tumor promoting esters have no colony stimulating ability. The mechanism of the colony stimulation by phorbol esters is not yet defined but does not seem to depend on the presence of detectable CSF or its production during the culture period. An overnight preincubation of marrow cells in CSF-free McCoy's medium, followed by addition of 125I-CSF, results in cellular binding of labeled

CSF over a 5 min -3 hr interval at 4C. Addition of unlabeled CSF during the preincubation phase abolishes subsequent binding of labeled CSF, apparently by occupying CSF binding sites. When 10-7M TPA was present during the preincubation phase, subsequent binding of labeled CSF was reduced by 83-87%, whereas addition of 10-7M phorbol reduced CSF binding by only 14-20%. The addition of 10-5M TPA to the preincubation medium also reduced subsequent CSF binding by greater than 80%, but TPA concentrations less than or equal to 10-9M had no effect. Preincubation of marrow cells with TPA leads to a marked inhibition of CSF binding while simultaneous addition of TPA and labeled CSF to marrow cells results in only modest inhibition of CSF binding. One explanation is that CSF and TPA may compete for CSF binding sites, but the sites may have a lower affinity for TPA than for CSF. The present experiments suggest that TPA may directly stimulate GM-CFC by a mechanism involving CSF binding sites. (no Refs)

64. ACTIVATION OF EPSTEIN-BARR VIRUS EXPRESSION IN LATENTLY INFECTED HUMAN LYMPHOBLASTOID CELLS WITH BACTERIAL FATTY ACIDS AND PROMOTORS OF PLANT AND MICROBIAL ORIGIN: A POSSIBLE CAUSE FOR BURKITT'S LYMPHOMA AND NASOPHARYNGEAL CARCINOMA (MEETING ABSTRACT).

Ito Y, Kishishita M, Yanase S, Kawanishi M, Takashima M, Imanaka H

No affiliation given

Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. The Association 187 pp., 1981.

When used in combination with 12-O-tetradecanol phorbol-13-acetate (TPA) and/or croton oil, even other common fatty acids like i-butyric acid and propionic acids also exherted marked Epstein-Barr virus (EBV)-inducing activity in nonproducer Raji cells. This led us to test the bacteria-produced short-chain fatty acids as EBV-inducers both with and without promotors and, found that the members of Fuso bacterium, Clostridium and other species, those which produce such compounds as their metabolites, indeed play a significant role in the activation of EBV expression as detected by EBV-early (EA) and -viral capsid antigens (VCA). On the other hand, the roots of croton oil, the parent compound of TPA, was traced back to a leafy shrub, Croton tiglium, a plant native to Southeastern Asia. Incidentally, we came across a fact that the seed from which croton oil is expressed has been used as herbal drug in Southern China for over 1000 yr. This prompted us to test other analogous extracts from the Euphorbiaceae family to which C tiglium belongs. The ether extracts prepared from all these Euphorbiacea plants proved to be an efficient EBV-inducers. The Euphorbiacea plants currently used as herbal medicaments amount to more than 30 species in Southern China and as much as 90 in East Africa. We have recently observed that an indol-alkaloid produced by a variant of Streptomyces mediocidius, Teleocidin B, also can act as a powerful inducer and activator of EBV with an efficiency comparable to TPA in our producer and nonproducer test system. (1 Ref)

65. 12-O-TETRADECANOYL-PHORBOL-13-ACETATE (TPA) DECREASES CHRONIC LYMPHOCYTIC LEUKEMIA B LYMPHOCYTE DNA NEGATIVE SUPERHELICITY TO NORMAL LEVELS (MEETING ABSTRACT).

Lipetz PD, Murphy MP, Jewett HD, Stephens RE

No affiliation given

Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. The Association 187 pp., 1981.

Chronic lymphocytic leukemia (CLL) B lymphocytes possess increased DNA negative superhelicity. Decreased eucaryotic DNA negative superhelicity results in decreased DNA synthesis and may be associated with the altered gene expression quantitated by DNase 1 sensitivity. Treatment of CLL B lymphocytes with a tumor-promoting agent, TPA, results in 'pseudo' differentiation manifesting as: 1) increased amounts of intracytoplasmic immunoglobin; 2) ultrastructural changes showing a maturation toward plasma cells; and 3) decreased DNA synthesis. This differentiation system varies from mitogen/Epstein-Barr virus induced differentiations in that DNA synthesis is decreased. TPA treatment (24 hr, 1.6 x 10(-7) M TPA in ETOH) of CLL B lymphocytes results in a reduction of the increased DNA negative superhelicity to a level comparable to normal lymphocytes. DNA negative superhelicity is proportional to the concentration of ethidium bromide (EB) which induces minimal sedimentation to nucleoids in EB-neutral sucrose gradients. CLL lymphocytes were verified by E-rosetting, EAC-rosetting, and surface immunoglobins. The observed decrease in DNA synthesis would be expected from decreased DNA negative superhelicity. (5 Refs)

66. [3H]THYMIDINE INCORPORATION IN BOVINE LYMPHOCYTES TREATED WITH THE TUMOR PROMOTE R, 12-O-TETRADECANOYL PHORBOL-13-ACETATE.

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Exp Cell Res; 135(2):267-276 1981

Treatment of bovine lymph node lymphocytes with the tumor promoter, 12-O-tetradecanoyl phorbol-13-acetate (TPA) leads to depressed [3H]thymidine incorporation in response to phytohemagglutinin (PHA). Radioautographic and morphological analyses showed that depression was at the level of blast-cell formation. Isotope-dilution experiments, and the use of [3H]deoxycytidine to label DNA indicated that the inhibition was not due to a block in thymidine transport in the treated cells. These experiments, as well as a bioassay designed to measure thymidine in the culture medium, showed that the apparent inhibition of [3H]thymidine incorporation and DNA synthesis was not the result of production of cold thymidine in the cultures. The results taken together support the idea that most TPA-treated cells are inhibited from responding to the mitogenic lectins. Those cells which do respond appear to form blast cells and synthesize DNA at the same rate as do untreated cells. (Author abstract) (24 Refs)

67. CELL CYCLE DEPENDENCY OF TUMOR PROMOTER ON MURINE ERYTHROLEUKEMIC CELLS (MEETING ABSTRACT).

Zucker RM
No affiliation given

Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. The Association 187 pp., 1981.

The tumor promoter 12-O-tetradecanoyl-phorbol-13-acetate (TPA) affected the cell cycle of murine erythroleukemic cells (MELC). In logarithmically growing cells a transient G1 block lasting approx 6 hr developed after the addition of TPA. To investigate this cell cycle effect of TPA, cells were synchronized either by a double thymidine block or by centrifugal elutriation and were analyzed by flow cytometry and electronic nuclear vol. Using double thymidine blocked synchronized cells or elutriated separated fractions containing cells other than G1, a transient G1 block occurred as the cell entered early G1. The G1 elutriated cell population was blocked in the G1 period by TPA prior to cell cycle traverse. This transient block in G1 was not observed after the next cell cycle traverse. Addition of TPA to butyric acid (BA) or dimethylsulfoxide (DMSO) induced cells resulted in a transient G1 block in addition ot inhibition of differentiation. TPA was more inhibiting on DMSO induced cells than BA induced cells. (no Refs)

68. TUMOUR PROMOTERS INDUCE MITOTIC ANEUPLOIDY IN YEAST.

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Dept. Genetics, Univ. Coll. Swansea, Singleton Park, Swansea SA2 8PP, England

Nature; 294(5838):263-265 1981

A series of seven phorbol analogues and eight unrelated compounds were tested fo r induction of aneuploidy or crossing-over in assays using the D6 strain of Saccharomyces cerevisiae. A positive response was a three-fold or greater increase in frequency of aneuploid colonies in at least two separate experiments. All promoters tested were positive, while nonpromoters were negative. 12-O-Tetradecanoylphorbol-13-acetate (TPA) and phorbol-12-13-didecanoate (PDD) were positive while no significant increases in aneuploidly were observed with phorbol, phorbol monoesters, 4-O-methyl-TPA or 4alpha-PDD, which are also inactive as promoters on mouse skin. A dose-response curve for TPA showed dose-related increases in aneuploidy over the concentration range 0.02-5.0 ug/ml. Mezerein, a weak promoter but as potent as TPA in inducing many biochemical and morphological effects in cells, did not induce aneuploidy in the assay. The tumor promoters had no effect on the frequency of crossing-over. However, under identical conditions, the incomplete promoter mezerein induced mitotic cross-over at concentrations greater than 10 ug/ml whereas TPA was ineffective. Mezerein was the only compound which showed significant activity in increasing cross-over. The data presented do not indicate whether the assay of induced chromosome aneuploidly in yeast will be useful in detection of tumor promoting chemicals. (27 Refs)

EPIDEMIOLOGIC DATA CONCERNING MODIFICATION OF CARCINOGENESIS

69. OVERVIEW: EPIDEMIOLOGICAL ASPECTS OF TUMOR PROMOTION (MEETING ABSTRACT).

Wynder EL
American Health Foundation, Valhalla, NY

International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

The causes of the main human cancers, namely those in the respiratory tract, the gastro-intestinal tract, and the endocrine-sensitive organs, especially breast and prostate, are complex and multifactorial. A major risk factor for respiratory tract cancers is tobacco, containing genotoxic carcinogens but, importantly also, cocarcinogens and promoters of diverse kinds including phenolic compounds. Cancers of the colon, breast, and prostate involve as yet unknown carcinogens, possibly related to the intake of mutagens in fried foods. The major contributing effect for these types of cancer is related to the level of dietary fat consumed which, in turn, through endogenous metabolism, generates proportional levels of bile acids, shown to be promoters in colon cancer, and of specific endocrine balances which appear to play a promoting role in cancer of the breast and prostate. Inasmuch as promotion is highly dose-dependent and reversible, there is evidence that alteration of the promotion phase of carcinogenesis may rapidly and effectively establish a lower risk situation. Individuals who stop smoking remove the pressure of promotion progres sively, thereby lowering their risk of lung cancer development. Individuals who consume food with higher cereal fiber or lower fat content decrease the effective concentration of bile acids and have reduced risk of colon cancer. In many instances, parallel confirmatory results have been obtained in animal models. Thus, there is hope that modulation of the promotion phases in specific promotion-dependent human carcinogenesis may permit a relatively rapid and effective reduction of risk. (no Refs)

70. EPIDEMIOLOGY - SHORTCOMINGS AND POSSIBILITIES (MEETING ABSTRACT).

Clemmesen J
Danish Cancer Registry, Copenhagen, Denmark

International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Epidemiology is at present in no position to make any substantial contribution distinguishing between initiator and promoter effects in human cancer, and it is the intention of the author to illustrate shortcomings of modern epidemiological means, and ways for their improvement, taking his start from the current discussion on conclusiveness of mortality versus morbidity data presented in June and July issues 1981 of Journal National Cancer Institute by Doll and Peto and Clemmesen. Data for tumors of the urinary bladder from American and Danish Cancer Registration versus mortality data and supplemented with data for other malignant neoplasms will serve as illustrations. Further it is pointed out that we are in need of an estimate as accurate as possible of the latent periods of human cancers of known origin, often occupational, and it is proposed that a committee is established with the task of going over such data as are available for the last 100 yr with a view to an assessment. (no Refs)

71. MODEL FOR HUMAN CARCINOGENESIS: ACTION OF ENVIRONMENTAL AGENTS (MEETING ABSTRACT).

Moolgavkar SH
Institute for Cancer Research, Philadelphia, PA
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Current statistical prescriptions for low-dosage extrapolation of carcinogenic risk make no distinction between exposure to initiators and exposure to promoters despite the abundant data that these two classes of carcinogens have different modes of action. One reason for this is the lack of an appropriate model. In this paper, a model for carcinogenesis is presented which provides a framework for understanding the roles of 'spontaneous' events, hereditary factors, and environmental agents in human carcinogenesis and for interpreting experimental carcinogenesis. This model incorporates two features: (1) transition of target stem cells into cancer cells via an intermediate stage in two irreversible steps, (2) growth and differentiation of normal target and intermediate cells. Cast in mathematical terms the model can be fitted to age-specific incidence data on human cancers of both children and adults and can illuminate the relative importance of agents that affect transition rates, tissue growth and tissue differentiation. Within the context of the model, initiators act by affecting the transition rates, whereas promoters influence the kinetics of growth, especially of initiated cells. The model provides a good quantitative description of the epidemiology of carcinomas of the breast and of the lung. The data are consistent with the notion that hormones and cigarette smoke act as promoting agents in carcinoma of the breast and of the lung respectively. (no Refs)

72. IMPLICATIONS OF PROMOTION AND ENHANCEMENT (MEETING ABSTRACT).

Higginson J
No affiliation given
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

The principles of public health legislation of potential hazards in the environment have developed through past experience on acute toxic hazards and communicable diseases. Regulatory legislation involving modification of human societies should be: 1) effective; 2) acceptable by the public; 3) in accord with the scientific evidence; 4) consistent; 5) flexible; and 6) not be counter-productive. Evidence that many cancers have multi-factorial origin and that carcinogenesis may be modulated by exogenous and endogenous factors prior to, during and after cell transformation, leads to complex regulatory problems. For many cancers, 'major avoidable risks' cannot be identified, and in these modulating factors whose action may be reversible, may be of pivotal etiological importance. However, without definite data on the comparative role of individual enhancers, promoters and inhibitors in the environment, logical legislation based on scientific data may be impossible, since both animal and human studies may only provide guidance as to the overall summated effect. It is concluded that where a defined promoting factor can be related to the causation of human cancer, regulation may be possible, eg postmenopausal estrogens. However, for most enhancers or promoters, eg dietary fat, enzyme inducers, etc knowledge is insufficient to allow generic regulation to meet the above objectives. Thus, regulatory action where desirable should be pragmatic, ad hoc and directed to (1) above. More research is clearly required. (no Refs)

73. FACTORS THAT PROMOTE THE DEVELOPMENT OF HUMAN BREAST CANCER (MEETING ABSTRACT).

Thomas DB
Fred Hutchinson Cancer Research Center, Seattle, WA
International Symposium on Health Effects of Tumor Promotion, October 12-15, 198 1, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

The epidemiologic features of breast cancer and current hypotheses regarding the etiologic role of endogeneous hormones are summarized and evaluated. The inconsistent results of studies of exogenous hormones and breast cancer are also critically summarized. A proposed model for human mammary carcinogenesis is presented. Hormonal aberrations that vary with reproductive and menstrual events are hypothesized to alter susceptibility of mammary tissue to primary carcinogens. The nature of these aberrations, and the identity of the primary carcinogens are largely unknown. Avenues for further research are suggested. (no Refs)

REVIEWS AND OTHER RELATED STUDIES

74. NUTRITION AND CANCER: A REVIEW.

Muller E, Rickenbach M
Institut fur Sozial- und Praventivmedizin, Universitat Zurich, Gloriastrasse 32 B, 8006 Zurich, Switzerland
Praxis; 70(43):1903-1912 1981

The possible roles of various nutrients in carcinogenesis are reviewed. Epidemiological studies indicate a high rate of carcinomas of the breast (BC) and colon (CC) in industrialized countries. Dietary factors are suggested by changes in cancer frequencies among immigrant populations and their descendants. Dietary studies indicate a positive correlation between dietary fat and CC and BC, as well as a negative correlation between these cancers and dietary fiber content. Animal studies have shown a cancer-promoting effect for fats, particularly unsaturated fats. Fats may promote cancer by affecting specific intestinal bacterial populations, bile secretion, hormonal balance, and immune response. Fiber may reduce cancer risk by speeding the movement of carcinogens through the digestive tract. Cancer risk has not been confirmed for proteins or their pyrolysis products. Some studies have indicated risk associated with pickled, smoked, or fried foods related to production of nitrosamines and nitrosamides. These compounds, which have been shown to be carcinogenic, are formed in vitro from nitrites and secondary amines. Their formation appears to be limited by the presence of ascorbic acid or vitamin E. Further studies of dietary factors are indicated. (130 Refs) (In GER)

75. DEPRESSED IMMUNITY AND THE DEVELOPMENT OF CANCER.

Penn I
Dept. Surgery, Univ. Colorado Health Sciences Center, 1035 Clermont St., Denver, CO, 80220
Clin Exp Immunol; 46(3):459-474 1981

Epidemiological, clinical, and experimental studies of depressed immunity and cancer are reviewed. Topics include transplantation of tumors, cancer in patients with naturally occurring immunodeficiency disorders, de novo cancer in organ transplant recipients, and cancer in uremic patients. Patients with autoimmune and other diseases treated with immunosuppressive agents have increased cancer incidence. Second

cancers, particularly leukemias, are more frequent in patients treated with chemo- and radiotherapy. Disturbances in immunity as causes of cancer are presented; immune surveillance, immune stimulation, chronic antigenic stimulation, defective immunoregulation, spontaneous regression of lymphomas, interferons, oncogenic viruses, oncogenic and co-oncogenic effects of immunosuppressive and cancer therapeutic agents, and other potentially oncogenic treatments (UV and arsenic for psoriasis) are discussed. Animals and patients vary in their susceptibility to oncogenic stimuli. Evidence suggests that the immune system plays a key role in host defense against cancer, but many unanswered questions remain. (149 Refs)

76. CHEMOPREVENTION OF CANCER WITH RETINOIDS.

Peck GL
Dermatology Branch, National Cancer Inst., Bulding 10, Room 12N238, Bethseda, MD, 20205
Gynecol Oncol; 12(2,part2):S331-S340 1981

Use of synthetic retinoids, isotretinoin (13-cis-retinoic acid, RO-4-378, Accutane) and an aromatic retinoid (etretinate, RO-10-9359, Tigason), in cancer prevention and therapy for cutaneous and internal tumors was reviewed. Etretinate and oral isotretinoin were used in treatment of basal cell carcinoma Etretinate was used in treatment of lesions of epidermodysplasia verruciformis induced by the oncogenic human papilloma virus (types 3 and 5), flat, genital, and plantar warts. Cutaneous metastases of malignant melanoma are tested with retinoids. Leukoplakia of the oral cavity, hyperkeratosis of the larynx, and papillomas of the urinary bladder have been treated with etretinate. Chemoprevention of cancer has been accomplished experimentally with chemically diverse agents (carotenoids, folic acid, butylated hydroxytoluene, butylated hydroxyanisole, selenium, ethoxyquin, disulfiram, vitamin E) Retinoids are known to inhibit tumor promotion. Predominant observed toxicities of synthetic retinoids in man involve the skin and mucous membranes. Systemic toxicities are arthralgia, temporary low-grade elevation of serum transaminases and teratogenicity. Observed acute toxicities were well tolerated and no chronic toxicities have been observed. (55 Refs)

77. SURFACE ACTIVE AGENTS AS TUMOR PROMOTERS (MEETING ABSTRACT).

Boyland E
London School of Hygiene and Tropical Medicine, London, England
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Initiation and promotion are different stages in carcinogenesis. Initiators are generally mutagenic and if a substance or procedure is carcinogenic and not mutagenic the effect is most probably tumor promotion. Many carcinogens are complete, having both initiating and promoting activity. Promoters alone induce tumors because initiators are present in the diet or the environment. Promoters can be physical as with trauma and foreign bodies such as with asbestos. Promoters are often organotropic; phenobarbitone, clofibrate and valium act on the liver of rodents. Of the 14 types of tumor promoters listed, the class of surfactants includes many different compounds. Saccharin, cyclamate and tryptophan act on the rat bladder, and lithocholic acid on the colon. The sweetening agents and bile acids reduce interfacial tension by some 20% in concentrations at which they are present in urine or feces when given in doses which promote tumors in rats. The incidence of cancer of esophagus and mouth is high in smokers who consume spirits rather than beer. The cigarette provides initiators and the alcohol acts as promoter. The alcohol present in spirits would reduce the interfacial tension appreciably in the mouth and esophagus so that the carcinogenic action of spirits is probably due to the promoting action of the alcohol because of its surface activity. With promoters of the surfactant type there are levels below which the effects are negligible and so there may be safe levels. This is clearly the concentration attained at any particular time rather than the total dose. The effect of the surface active tumor promoters is probably due to action on cell membranes. The mode of action of solvents such as chloroform and benzene is probably similar. There must be safe or threshold levels for the surface active and other promoters, but probably not for materials like asbestos which remain in the body. It is possible that there are no safe levels for initiators, but if there were they might vary with exposure to promoters. (no Refs)

78. LIVER CARCINOGENESIS: THE ROLE FOR SOME CHEMICALS OF AN EPIGENETIC MECHANISM OF LIVER-TUMOR PROMOTION INVOLVING MODIFICATION OF THE CELL MEMBRANE.

Williams GM
Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595
Food Cosmet Toxicol; 19(5):577-583 1981

A number of chemicals, including phenobarbitals, DDT, and polychlorinated biphenyl, are hepatocarcinogenic in mice and rats after prolonged exposure; they lack genotoxic action and have been suggested to be epigenetic carcinogens. Because several of these chemicals enhance the effect of genotoxic carcinogens under conditions in which they are not themselves carcinogenic, they are probably of the promoter class of epigenetic carcinogens. Mechanism of promotion may involve (1) completion of conversion of partially transformed cells to full neoplastic cells, or (2) inhibition by the promoter of intercellular communication. The first mechanism has been demonstrated in skin-tumor promoters (phorbol esters and teleocidin B), whereas the latter mechanism has been demonstrated in studies in which tumor promoters inhibited intercellular communication in fibroblast- and liver-cell cultures. Inhibition by DDT of metabolic cooperation between hepatocytes and adult rat-liver epithelial-thioguanine-resistant mutant cells is described. The theory that tumor promoters interfere with transmission of regulatory factors from normal to spontaneously transformed cells is consistent with the dose-response characteristics of epigenetic promoter hepatocarcinogens. (37 Refs)

79. EPIGENETIC MECHANISMS OF LIVER TUMOR PROMOTERS AND IMPLICATIONS FOR HEALTH EFFECTS (MEETING ABSTRACT).

Williams GM
American Health Foundation, Valhalla, NY
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Cells in vivo and in vitro exchange molecules through specialized membrane organelles known as gap junctions. Intercellular transfer of growth and/or differentiation regulating factors could be involved in suppressing the growth of initiated neoplastic cells. Several liver tumor promoters have been found to inhibit intercellular communication in an in vitro liver culture system. This effect on the cell membrane could thus, be the basis for the tumor promoting activity of these chemicals. Such an epigenetic mechanism would account for the requirement for high doses and prolonged exposure for certain liver

tumor promoters. In addition, it implies a distinct type of health risk analysis. A number of chemicals particularly halogenated hydrocarbons, produce primarily or exclusively an increase in liver tumors in rodents which display a spontaneous incidence of such tumors. Several of these chemicals exert an inhibition of intercellular communication and thus, may be functioning as liver tumor promoters. Accordingly, the health risk analysis for these chemicals is different from that for genotoxic carcinogens. (no Refs)

80. THE CURRENT USE OF STUDIES ON PROMOTERS AND COCARCINOGENS IN QUANTITATIVE RISK ASSESSMENT (MEETING ABSTRACT).

Stara JF
U.S. Environmental Protection Agency, Cincinnati, OH
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Under the Clean Water Act, the US Environmental Protection Agency is required to develop an approach for controlling the release of hazardous pollutants in water. As part of this effort, the Environmental Criteria and Assessment Office (ECAO) in Cincinnati, with the support of other groups in the Office of Health and Environmental Assessment (OHEA), was assigned the task of assessing the potential health risks associated with contamination of the aquatic environment. Initially, ECAO's major responsibility was to prepare the Human Health Effects Assessment Chapters of the 65 Ambient Water Quality Criteri a Documents (AWQCDs) which were required under the Consent Decree of Environmental Defense Fund vs Train. Along with scientists from other Agency offices, academia, and private sector, ECAO developed guidelines for deriving ambient water quality criteria and applied these guidelines to the available data on the 129 compounds included in the 65 documents. Several of the pollutants covered in these documents have been shown to be promoters or cocarcinogens. For example, phenol appears to have tumor promoting activity in mice when repeatedly applied after initiation with either dimethylbenzanthracene (DMBA) or benzo(a)pyrene (BaP). Similarly, it has recently been reported that 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is a potent liver promoter and a cocarcinogen. However, it became apparent that satisfactory methods had not yet been developed for using promotion/cocarcinogenicity data in quantitative risk assessment. For this reason, the derived criteria for some pollutants with promotion/cocarcinogenic activities were based on carcinogenicity, toxicity, and organoleptic effects. (no Refs)

81. THE DECISION-POINT APPROACH FOR SYSTEMATIC CARCINOGEN TESTING.

Weisburger JH, Williams GM
Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595
Food Cosmet Toxicol; 19(5):561-566 1981

The decision-point approach provides a framework, based on current concepts of the mechanisms of carcinogenesis, for systematic evaluation of potential mutagenic and carcinogenic hazards of chemicals. Chemical carcinogens have been divided into two main categories-genotoxic agents, which interact with DNA and genetic material and lead to irreversible alterations in DNA, and epigenetic agents, which operate by distinct nongenotoxic mechanisms and are tissue-specific. Genotoxic agents include direct-acting carcinogens, procarcinogens, and inorganic carcinogens; the first two classes damage DNA either through direct chemical reactivity or following metabolism by enzyme systems, whereas inorganic carcinogens are not directly genotoxic but lead to changes in DNA by selective alteration in the fidelity of DNA replication. Epigenetic agents include solid-stage carcinogens, hormones, immunosuppressors, co-carcinogens, and promoters. The decision-point approach involves five steps: (1) consideration of the structure of the chemical; (2) in vitro short-term tests (mutagenesis, DNA repair, chromosome effects, and cell transformation); (3) limited in vivo bioassays (skin-tumor induction in mice, pulmonary-tumor induction in mice, breast-cancer induction in rats, induction of rodent liver altered foci, and assays for promoters); (4) chronic bioassay; and (5) final classification of a chemical as a genotoxic or epigenetic carcinogen. Health-risk analysis also must consider quantitative potential as well as qualitative positive or negative results. The proposed testing approach provides for systematic yet economical testing, the results of which can be applied to flexible, rational health-risk analysis. (26 Refs)

82. AN APPROACH TO ESTIMATING CANCER RISKS IN HUMANS AND FORMULATING PERMISSIBLE LIMITS OF EXPOSURE TO GENOTOXIC CARCINOGENS BASED ON A TWO STAGE INITIATION-PROMOTION CARCINOGENESIS MODEL (MEETING ABSTRACT).

Albert R, Burns F, Altshuler B
New York University Medical Center, New York, NY
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Evidence is presented that the linear non-threshold dose-response relationship applies to the initiation stage of carcinogenesis, and to the interaction of carcinogen with DNA. At very low levels of exposure, it is expected that the initiation component of carcinogen action would be the action of major concern. This in turn leads to the consideration that for genotoxic carcinogens, only estrinsically or intrinsically promoted target tissues in humans would be at risk. An approach is presented based on these considerations for carcinogen risk assessment and for setting upper limits for acceptable carcinogen exposure in terms of life span shortening. (no Refs)

83. REGULATING TUMOR PROMOTERS: THE INTERACTION OF SCIENCE AND POLITICS (MEETING ABSTRACT).

Williams JR
The George Washington University, Washington, DC
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Tumor promoters, as other carcinogens, present a potential human health hazard. The real extent of that hazard is unknown. The process by which resources and regulatory attention are directed toward tumor promoters is dependent upon scientific, political and economic factors. Of paramount importance in the interaction of these factors is the selection of particular biological tests as surrogates for human response to chemicals; tests for use by chemical manufacturers, or for regulatory purpose by federal agencies. This selection of tests, in turn, depends upon the degree to which a demonstrable consensus exists that the biology of a test portrays, at least to an appreciable extent, the pathology of concern, and/or that the test has predictive value as demonstrated by a verified data base. Political factors which impinge on this selection include the cost of the test, the availability of testing resources, the consideration of particular chemicals of economic or symbolic

value, and the combination of factors which produce the posturings both of the regulated and of federal agencies. Unless there is better definition of the essential molecular and cellular nature of cancer promotion, predictable by an inexpensive test, it is most unlikely that a meaningful screening of new or old chemicals for promotion will take place. In the absence of a scientific consensus for a methodology for evaluating promoters in the long-term whole animal bioassay, it is unlikely that commercial chemicals will be regulated to any extent based on a cancer-promoting activity. (no Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

DIETARY FACTORS IN CARCINOGENESIS

1. NUTRITION AND ENVIRONMENTAL HEALTH: THE INFLUENCE OF NUTRITIONAL STATUS ON POLLUTANT TOXICITY AND CARCINOGENICITY. VOLUME 2: MINERALS AND MACRONUTRIENTS.

Calabrese EJ

Environmental Health Program, Div. Public Health, Univ. Massachusetts, Amherst, MA

Nutrition and Environmental Health: The Influence of Nutritional Status on Pollutant Toxicity and Carcinogenicity. Volume 2: Minerals and Macronutrients. New York, John Wiley and Sons, 468 pp., 1981.

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

2. RETROSPECT AND PROSPECT OF STUDIES ON DIGESTIVE SYSTEM DISEASES IN CHINA.

Zhang X

Dept. Internal Medicine, Capital Hosp., Chinese Acad. Medical Sciences, Beijing, People's Republic of China

Zhonghua Xiaohua Zazhi; 1(1):1-4 1981

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3. EPIDEMIOLOGY OF PITUITARY ADENOMAS.

Gold EB

Dept. Epidemiology, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 Wolfe St., Baltimore, MD, 21205

Epidemiol Rev; 3:163-183 1981

4. BLADDER CANCER EPIDEMIOLOGY.

Matanoski GM, Elliott EA

Dept. Epidemiology, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 North Wolfe St., Baltimore, MD, 21205

Epidemiol Rev; 3:203-229 1981

5. THE EPIDEMIOLOGY OF BENIGN BREAST DISEASE.

Ernster VL

Dept. Epidemiology and International Health, 1699HSW, Univ. California, San Francisco, CA, 94143

Epidemiol Rev; 3:184-202 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

6. AIR POLLUTION AND BIOLOGICAL DEFENCE.

Schlipkoter HW, Dolgner R

Med. Institut fur Umweithygiene an der Univ., Gurlitttrasse 53, D-4000 Duesseldorf 1, W. Germany

Zentralbl Bakteriol [Orig A]; 172(4/5):299-311 1981

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7. CANCER AND THE PHYSICOCHEMICAL QUALITY OF DRINKING WATER IN QUEBEC.

Thouez JP, Beauchamp Y, Simard A

Dept. Geography, Univ. Montreal, Montreal, Quebec, Canada

Soc Sci Med [Med Geogr]; 15(1):213-223 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

8. ONCOGENIC VIRUSES.

Wyke JA

Imperial Cancer Res. Fund, P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England

J Pathol; 135(1):39-85 1981

9. ROLE OF VIRUSES IN THE ETIOLOGY OF NATURALLY OCCURRING FELINE LEUKEMIA.

Essex M, Grant CK, Cotter SM, Hardy Jr WD

Dept. Microbiology, Harvard Sch. Public Health, 665 Huntington Ave., Boston, MA, 02115

Haematol Blood Transfus; 26:483-487 1981

METHODOLOGY IN CARCINOGENESIS RESEARCH

10. MAMMALIAN IN VIVO AND IN VITRO CYTOGENETIC ASAYS: A REPORT OF THE U.S. EPA'S GENE-TOX PROGRAM.

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Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830

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MODIFICATION OF CARCINOGENESIS BY CHEMICAL AGENTS OR IRRADIATION

1. ENHANCEMENT OF HEPATOCARCINOGENESIS BY SEQUENTIAL ADMINISTRATION OF CHEMICALS: SUMMATION VERSUS PROMOTION EFFECTS.

Williams GM, Katayama S, Ohmori T
American Health Foundation, Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595
Carcinogenesis; 2(11):1111-1117 1981

A comparative study was made of the sequential administration of the liver carcinogen, diethylnitrosamine (DEN), or the liver tumor promoter, phenobarbital, given after the liver carcinogen, N-2-fluorenylacetamide (FAA). The effects of the

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second carcinogen on preneoplastic cellular lesions induced by the first carcinogen were comparable to the effects of the promoter. In addition, both sequential exposures enhanced the ultimate carcinogenic effect, although the combination of FAA followed by DEN resulted in a greater number of malignant neoplasms. Thus, enhancement of carcinogenesis by a second chemical cannot be used by itself as evidence of a promoting action. Approaches to the more precise definition of promoters include exclusion of genotoxicity, identification of epigenetic mechanisms and lack of a summation effect with administration prior to genotoxic carcinogens. (Author abstract) (50 Refs)

2. COMPARISON OF THE EFFECT OF BUTYLATED HYDROXYTOLUENE ON N-NITROSOMETHYLUREA AND 7,12-DIMETHYLBENZ(A)ANTHRACENE-INDUCED MAMMARY TUMORS.

King MM, McCay PB, Kosanke SD
Biomembrane Res. Lab., Oklahoma Medical Res. Foundation, 825 N.E. 13th St., Oklahoma City, OK, 73104
Cancer Lett; 14(3):219-226 1981

The effects of butylated hydroxytoluene (BHT) on nitrosomethylurea (NMU)- and 7,12-dimethylbenz(a)anthracene (DMBA)-induced rat mammary tumors were examined. Female Sprague-Dawley rats were fed either control diets or diets plus 0.3% BHT, and further divided into NMU-treated, DMBA-treated, or nontreated groups. DMBA was administered at 10 mg in 1 ml stripped corn oil intragastrically at 50 days of age. NMU was administered at 5 mg/100 g body wt iv in the tail vein at 50 days of age. A 100% incidence of tumors was seen in rats treated with DMBA and on the control diet. The incidence was reduced to 54% by addition of BHT to the diet. No difference in tumor incidence was seen in NMU-treated animals with or without addition of BHT. The differences in tumor prophylaxis may reflect the fact that DMBA is metabolized by the monooxygenase system but NMU is not. (30 Refs)

3. EFFECT OF RETINOIDS ON THE INDUCTION OF COLON CANCER IN F344 RATS BY N-METHYL-N-NITROSOUREA OR BY 1,2-DIMETHYLHYDRAZINE.

Silverman J, Katayama S, Zelenakas K, Lauber J, Musser TK, Reddy M, Levenstein MJ, Weisburger JH
American Health Foundation, Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595
Carcinogenesis; 2(11):1167-1172 1981

The possible modifying effect of synthetic and natural retinoids on the incidence of colon cancer in rats induced by two intrarectal doses of 2.5 mg of N-methyl-N-nitrosourea (MNU) given once a wk for 2 successive wk or a single 150 mg/kg body weight dose of 1,2-dimethylhydrazine (DMH), sc was investigated. Emphasis was on the effect of the development of early tumors as visualized by endoscopy. With the retinoids N-ethyl-retinamide, N-2-hydroxyethylretinamide, N-(4-hydroxyphenyl)-all-trans-retinamide (RAHA) and retinyl acetate (RA) administered orally after the carcinogens, significant differences in early developing tumors were not found. At histopathological examination of the tumors the RAHA + DMH group had significantly fewer adenomas per animal. The percentage of adenoma bearing rats was significantly lower in groups receiving RAHA + DMH or RA + DMH. However, food consumption was lower in rats consuming either RAHA or RA Retinyl palmitate (RP) and RAHA were administered intrarectally to MNU-induced rats either before or after the carcinogen. When administered before MNU, RP caused a significant increase in the percentage of tumor bearing animals and the av number of tumors per animal as visualized endoscopically. At histopathological examination, all retinoid groups except RAHA given after the carcinogen, produced significantly more adenomas per animal and a significantly greater adenoma incidence than did the control groups. Thus, in two systems, the oral administration of retinoids did not clearly inhibit the early or later stages of colon tumor development. Intrarectal infusion of two retinoids had no effect on colonic morphology but at histopathological examination of later stage tumors there was an enhanced adenoma response. (Author abstract) (36 Refs)

4. EFFECTS OF THREE RETINOIDS ON COLON ADENOCARCINOMAS, SARCOMAS AND HYPERPLASTIC POLYPS INDUCED BY INTRARECTAL N-METHYL-N-NITROSOUREA ADMINISTRATION IN MALE F344 RATS.

Wenk ML, Ward JM, Reznik G, Dean J
Microbiological Assoc., Inc., 5221 River Road, Bethesda, MD, 20816
Carcinogenesis; 2(11):1161-1166 1981

Male F344 rats, 9 wk of age, were given multiple intrarectal administrations of N-methyl-N-nitrosourea (NMU) at 0.5 mg/dose twice a wk for a total of 8, 12, or 16 doses. Five days after the final NMU instillation, rats were placed on one of four diets; chow with retinoid vehicle, chow with 654 mg N-ethylretinamide per kg diet, chow with 686 mg N-(2-hydroxethyl)retinamide per kg diet, or 406 mg retinylidene dimedone per kg diet. Groups of 40-50 rats receiving 16, 12, or 8 total doses were sacrificed 32, 44, or 52 wk after the initial NMU dose, respectively. The number of rats with colon tumors and the number of tumors per tumor bearing rat in each dosage regimen was compared to appropriate controls. Organ weights for testis, liver, and kidneys were similar for controls and retinoid treated animals and no histopathologic lesions indicative of retinoid toxicity were found. Unusual proliferative lesions of the colon in rats of all dosed groups included hyperplastic and inflammatory polyps and sarcomas. The feeding of diets containing these three retinoids did not significantly modify the incidence or multiplicity of colon tumors observed under these conditions. (Author abstract) (18 Refs)

5. DIAPLACENTAL INITIATION OF NMRI MICE WITH 7,12-DIMETHYL-BENZ[A]ANTHRACENE DURING GESTATION DAYS 6-20 AND POSTNATAL TREATMENT OF THE F1-GENERATION WITH THE PHORBOL ESTER 12-O-TETRADECANOYLPHORBOL-13-ACETATE: TUMOR INCIDENCE IN ORGANS OTHER THAN THE SKIN.

Goerttler K, Loehrke H, Hesse B, Milz A, Schweizer J
Inst. Experimental Pathology, German Cancer Res. Center, Im Neuenheimer Feld 280, D-6900 Heidelberg 1, W. Germany
Carcinogenesis; 2(11):1087-1094 1981

The tumor spectrum and tumor incidence in organs other than the skin were investigated in the 12-O-tetradecanoylphorbol-13-acetate (TPA) treated F1-generation of 13 groups of NMRI mice which had been initiated by a single intragastric dose of 7,12-dimethylbenz[a]anthracene during Days 6,8, and 10-20 of pregnancy. Promotion by topical application of TPA to the back skin was carried out twice per wk 12 wk after birth over a period of 26 wk. The forestomach epithelium represented the only organ in which statistically significant 2-stage carcinogenesis could be demonstrated. A promotion effect could be seen in tumors of the Harderian gland, of the liver of male animals and on the development of both benign and malignant tumors of the lung in both sexes. Promo-

tion treatment therefore led to an activation of initiated tumor cells in those organs in which a very sensitive, more or less narrowly spaced oncogenic determination period exists. (Author abstract) (12 Refs)

MODIFICATION OF CARCINOGENESIS BY HORMONAL OR GENETIC FACTORS

6. EFFECT OF NEONATAL CASTRATION ON LIVER TUMOR INDUCTION BY N-2-FLUORENYLACETAMIDE IN SUCKLING BALB/C MICE.

Toh YC
Dept. Physiology, Univ. New England, Armidale, New South Wales 2351, Australia
Carcinogenesis; 2(11):1219-1221 1981

BALB/c mice were castrated at 2 days of age and control animals were sham-operated. Untreated male and female mice were also included for comparison. One-half of the mice in each group were fed on alternate days with 1.5% N-2-fluorenylacetamide suspended in 1% gelatine by stomach tube beginning 1 wk of age for a total of 14 feedings. The experiment was terminated when the mice reached 1 yr old. Approx 30% of the male mice, but none of the females, developed liver tumors in groups fed carcinogen. This male predominance in the incidence of hepatocellular carcinomas was completely abolished when the animals were castrated neonatally. No lesions were observed in the liver of mice treated with gelatine suspension alone except one with neoplastic nodule. Although it has been observed that liver tumors are produced more readily in younger than in older mice, the present investigation shows that male hormonal environment during early life is more important than the age on the development of liver tumors initiated by carcinogen. (Author abstract) (21 Refs)

STUDIES OF TUMOR PROMOTION OR COCARCINOGENESIS IN MOUSE SKIN

7. INHIBITION OF METHYLCHOLANTHRENE-INDUCED SKIN CARCINOGENESIS IN HAIRLESS MICE BY DIMETHYL SULFOXIDE.

Iversen OH, Thorud E, Volden G
Inst. Pathology, Univ. Oslo, Oslo 1, Norway
Carcinogenesis; 2(11):1129-1133 1981

Hairless mice were given five topical applications of 470 nmol 20-methylcholanthrene (MCA) at 1 wk intervals. In one experimental group the MCA was dissolved in reagent grade acetone alone, in another group it was dissolved in a mixture consisting of 50% acetone and 50% dimethyl sulfoxide (DMSO). A control group received the mixed solvent alone. The animals were observed for development of papillomas and malignant tumors during 75 wk. The group treated with MCA in acetone/DMSO had a higher mortality than the two other groups. The admixture of 50% DMSO to the solvent had a significant inhibitory effect on tumor and cancer rates and on cancer yield, whereas no effect could be observed on the tumor yield. Hence, 50% DMSO in the solvent has a moderate, but significant, inhibitory effect on MCA-induced skin carcinogenesis. Similar inhibitory effect of DMSO on the promotion phase in two stage-carcinogenesis protocols have been reported in the literature. The biochemical mechanisms behind this effect are unknown. (Author abstract) (15 Refs)

8. PHENOLS AND OTHER COMPONENTS OF OIL SHALE TARS AND ASBESTOS AS FACTORS MODIFYING THE CARCINOGENIC ACTION OF BENZO(A)PYRENE.

Bogovski P, Kung A, Winkmann F
Inst. Experimental and Clinical Medicine, Hiiu Str. 42, 200016 Tallin, USSR
Arch Geschwulstforsch; 52(1):49-55 1982

The modifying action of phenols and other components (paraffins, olefins, naphthenes, aromatic hydrocarbons, neutral oxygen compounds) present in oil shale tar on the carcinogenic effects of benzo(a)pyrene (BP) and chrysotile asbestos dust was studied. Epicutaneous tests were performed on 500 C57Bl mice divided to 10 different treatment groups. The skin tumors found in this series included benign papillomas and malignant squamous epithelial carcinomas and basalomas. The tar fractions containing phenols and neutral oxygen compounds moderately potentiated the tumor-inducing action of BP, while the tar components alone induced at best papillomas. Another experimental series with 500 2.5-3-mo-old rats treated with BP, tar fractions and asbestos dust intratracheally revealed that the lung tumor incidence was highest after simultaneous administration of BP, asbestos dust and tar phenols. Asbestos dust potentiated the carcinogenic action of BP to the same extent as the tar phenols, whereas the latter had no such effect on the potency of asbestos dust. The lung tumors included epidermoid carcinomas, bronchial and alveolar adenocarcinomas and reticulosarcomas. (9 Refs) (In GER)

9. DIFFERENTIATION MODULATES THE RESPONSE OF GUINEA PIG EPIDERMAL KERATINOCYTES TO THE STIMULATION OF DNA SYNTHESIS BY TPA.

Delescluse C, Bourin MC, Furstenberger G, Marks F, Prunieras M
INSERM Unit U-212, Fondation A. De Rothschild, F-75019 Paris, France
Differentiation; 20(1):87-91 1981

Repeated applications of the phorbol ester 12-O-Tetradecanoyl-phorbol-13-acetate (TPA) to adult mouse skin initiated with a polycyclic hydrocarbon results in permanent epidermal hyperplasia and leads to tumor promotion. One application of TPA induces both DNA synthesis in the epidermis and morphological changes in suprabasal normally nondividing epidermal cells that have been interpreted as reprogramming of maturing keratinocytes that would be sent back into cycle. To investigate whether DNA synthesis is directly linked with promotion, single doses of TPA (20 nmol) were applied to the skin of guinea pig, an animal in which TPA does not promote tumor. A fourfold increase in DNA synthesis was detected at 24 hr by liquid scintillation counting after 3H-TdR in vivo incorporation. A 10-15-fold increase was noted at the same time by autoradiography. To see if TPA is able to initiate DNA synthesis in suprabasal keratinocytes, basal cells were isolated from suprabasal elements by the sequential action of trypsin. Basal cells in suspension were detected by immunofluorescence using bullous pemphigoid (BP) antibodies. Basal and suprabasal cell suspensions contained 70 +-4.5 and 23 +-8% BP-positive cells, respectively. Both cell suspensions were cultured in vitro 4-5 days. TPA (10(-7) M) was added to the culture medium 20 hr after seeding the cells and removed 24 hr later. The incorporation of 3H-TdR into DNA was measured daily. A 10fold increase in DNA synthesis was observed 3 days after treatment in basal cell cultures, whereas no significant effect could be de-

tected in suprabasal cultures from day 1-4. It is concluded that: (i) if DNA synthesis is necessary for promotion to occur, it is not sufficient; (ii) the effect of TPA on epidermal DNA synthesis is probably the result of an increase in the number of basal cells entering S phase, and not the consequence of the reprogramming of suprabasal maturing keratinocytes. (Author abstract) (14 Refs)

10. DIMINUTION OF MOUSE EPIDERMAL SUPEROXIDE DISMUTASE AND CATALASE ACTIVITIES BY TUMOR PROMOTERS.

Solanki V, Rana RS, Slaga TJ
Biology Div., Cancer and Toxicology Program, Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Carcinogenesis; 2(11):1141-1146 1981

The effects of phorbol ester tumor promoters and related compounds on superoxide dismutase (SOD) and catalase were examined. The treatment of adult mouse skin with 2 ug 12-O-tetradecanoylphorbol-13-acetate (TPA) resulted in a sustained decrease in the basal levels of both SOD and catalase activities in the epidermis. A decline in SOD activity occurred within 3 hr after application and the maximum effect was seen at 16-17 hr. The decrease in SOD activity was always accompanied by a similar decline in the epidermal catalase activity. The alterations in both enzymes occurred against a high background of enhanced protein synthesis which indicates that the effect of TPA is selective for SOD and catalase. Other tumor promoters such as phorbol 12,13-dibutyrate and the non-phorbol tumor promoter anthraline also lowered the activities of both the enzymes. Mezerein, a resiniferonol derivative with weak promoting activity but a potent Stage-II promoter, appeared to be more potent than TPA in lowering the basal levels. These results indicate that damage which favors neoplastic progression could occur in TPA-treated mouse skin due to the accumulation of free radicals resulting from low levels of SOD and catalase activity. In addition, the TPA-caused decrease in the levels of SOD and catalase was not prevented by either retinoic acid, fluocinolone acetonide, tosyl amino-2-phenylethyl chloromethyl ketone, or butylated hydroxytoluene, suggesting that inhibition of tumor promotion by these agents is not mediated through alterations in the levels of enzymatic activities which decrease free radical concentrations. (Author abstract) (29 Refs)

11. PHOSPHOLIPASE ACTIVITY IN SKIN AFTER APPLICATION OF PHORBOL ESTERS AND 3-METHYLCHOLANTHRENE.

Bresnick E, Bailey G, Bonney RJ, Wightman P
Dept. Biochemistry, Vermont Regional Cancer Center, Lake Champlain Cancer Res. Assoc., Univ. Vermont Coll. Medicine, Burlington, VT, 05405
Carcinogenesis; 2(11):1119-1122 1981

Topical administration of the promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA), is accompanied by an increased incorporation of [3H]arachidonic acid into mouse skin and a very significant activation of epidermal cell membrane phospholipase A2 without affecting intracellular acid phospholipase. Similar enhancement in epidermal cell phospholipase A2 was observed after application of phorbol-12,13-didecanoate or 3-methyl-cholanthrene to mouse skin. A small but significant increase in phospholipase A2 activity is also seen after application of the nonpromoter irritant, acetic acid. The elevated levels of the prostaglandins observed in mouse skin after topical application of promoters are probably triggered by the activation of this membrane enzyme. (Author abstract) (25 Refs)

CELL CULTURE STUDIES OF MECHANISMS OF MODIFICATION

12. EXPRESSION OF INITIATED AND PROMOTED STAGES OF IRRADIATION CARCINOGENESIS IN VITRO.

DiPaolo JA, DeMarinis AJ, Evans CH, Doniger J
Lab. Biology, NCI, Bethesda, MD, 20205
Cancer Lett; 14(3):243-249 1981

The temporal dynamics of 12-O-tetradecanoylphorbol-13-acetate (TPA)-promoted transformation in vitro and the sensitivity of initiation and promotion to lymphotoxin were investigated. Syrian hamster embryo cells (HEC) initiated by x-irradiation (300 R) were treated with TPA 48 hr later for transformation induction. TPA treatment resulted in a 15-20x enhancement of x-ray induced transformation. When cells were irradiated on day 1 and treated with TPA on days 3, 4, or 5 of the 7-day experiment, similar transformation frequencies resulted, indicating that TPA is required only for the last 2 days. All cells ap peared to be initiated on day 3. However, the presence of TPA from days 3-5 was found to be insufficient for max transformation. Since a return to levels of transformation obtained by x-irradiation alone occurs with decreasing intervals of TPA exposure, the promotion phenomenon is apparently reversible. Both TPA-dependent and TPA-independent initiation occurs after x-irradiation in this system. Lymphotoxin was found to inhibit TPA enhancement of UV or x-irradiation transformation of HEC. (15 Refs)

13. HYPERTHERMIC MODULATION OF X-RAY-INDUCED ONCOGENIC TRANSFORMATION IN C3H 10T1/2 CELLS.

Clark EP, Hahn GM, Little JB
Dept. Radiation Medicine, Massachusetts General Hosp., Boston, MA, 02114
Radiat Res; 88(3):619-622 1981

The effect of hyperthermia on the malignant transforming potential of x-rays was studied in the C3H mouse embryo cell line (10T1/2, clone 8). No transformed foci developed in non-treated cultures or in cultures exposed to hyperthermia alone. When hyperthermia was combined with x-rays, either a 43 C/60 min or a 45 C/15 min hyperthermic exposure preceding a 200-rad x-ray exposure, produced a 4-5-fold enhancement in mean transformation frequency as compared with that induced by x-rays alone. The yield of transformants for cells exposed to 200 rad following incubation at 43 C for 60 min was significantly higher than for those exposed to 200 rad alone (0.02 less than P less than 0.05). Heating times were important since shorter hyperthermic exposures did not result in transformation frequencies significantly higher than that induced by x-rays alone. A similar trend was also observed when transformation was scored on a per dish basis. The results suggested that the possibility of treatment-induced neoplasms should be considered before the design of combined hyperthermia-radiation treatment plans. (10 Refs)

14. GROWTH STIMULATION OF MICROENVIRONMENT-DEPENDENT MOUSE LEUKEMIAS BY TUMOR-PROMOTING PHORBOL ESTERS.

Hiai H, Nishizuka Y
Lab. Experimental Pathology, Aichi Cancer Center Res. Inst., Chikusa-ku, Nagoya 464, Japan
JNCI; 67(6):1333-1340 1981

The effects of 12-O-tetradecanoylphorbol 13-acetate (TPA) and related tumor-promoting phorbol esters on 23 symbiotic cell lines from AKR thymic leukemias were studied. The phorbol derivatives with in vivo cocarcinogenic activity increased the viable yield of leukemia cells of most symbiotic cell lines in the absence of growth-supporting adherent cells. Particularly, in 10 cell lines remarkable growth stimulation was observed with 1 to 10 ng TPA/ml. The effect of TPA was reversible, since the leukemia cells exposed to TPA for 48 hr failed to grow without TPA or adherent cells. The leukemia cells from a symbiotic cell line could be maintained in TPA-containing medium for as long as 8 wk without losing depend ence. The leukemia cells were refractory to growth stimulation by TPA after they acquired the capability to grow independently. Furthermore, by affecting the leukemia cells, TPA and active tumor promoters inhibited pseudoemperipolesis (ie, localization of leukemia cells under or between adherent cells), which is the basic cell interaction in symbiotic complexes. These effects of tumor-promoting phorbol esters are discussed with a special reference to the multistage hypothesis of leukemogenesis. (Author abstract) (56 Refs)

15. PHORBOL ESTERS STIMULATE THE RAPID RELEASE OF CHOLINE FROM PRELABELED CELLS.

Mufson RA, Okin E, Weinstein IB
Div. Environmental Sciences and Cancer Center/Inst. Cancer Res., Coll. Physicians and Surgeons, Columbia Univ., 701 West 168th St., New York, NY, 10032
Carcinogenesis; 2(11):1095-1102 1981

Evidence implicating the cell surface membrane as the primary site of action of phorbol ester tumor promoters has led us to characterize early changes in phospholipid metabolism which occur in response to these compounds. When C3H10T1/2 mouse embryo fibroblasts were incubated with [3H]choline for 24 hr, approx 78% of the cell associated material was found in phosphatidyl choline and the remainder in sphingomyelin and the acid soluble pool. Within 5 min of exposure of these prelabeled cells to the potent tumor promoter 12-O-tetradecanoyl-phorbol-13-acetate (TPA) the release of water soluble [3H]choline metabolites from cells into the medium was enhanced two-fold and by 60-120 min the release was 2-5 times that found in control cultures. The released material was identified by chromatography as choline and phosphoryl choline. Evidence was obtained that this material was not derived exclusively from the acid soluble pool or from the degradation of labeled sphingomyelin. Choline metabolite release was concentration dependent between 10(-8) and 10(-7) M TPA and was not associated with cell toxicity. Phorbol-12,13-didecanoate (PDD) was also active but 4alphaPDD, which is not a tumor promoter, was inactive. Neither cycloheximide (4-40 ug/ml) nor cordycepin (4-40 ug/ml) blocked the TPA induced release. The release was, however, temperature sensitive and did not occur at 4 C. TPA did not induce the release of [3H]inositol from prelabeled phosphatidyl inositol. Although, the calcium ionophore A23187 induced the release of arachidonic acid from prelabeled cells it did not induce choline release. In addition, 5,8,11,14-eicosatetraynoic acid, which inhibits both lipooxygenase and cyclooxygenase activity, did not inhibit TPA stimulation of choline release. We propose that the binding of TPA to cell surface receptors leads to a rapid activation of membrane associated phospholipase(s) that specifically degrade phosphatidyl choline. This effect may be analogous to the ability of other agonists to activate degradation of phosphatidyl inositol. (Author abstract) (38 Refs)

16. INTERACTION OF PHORBOL ESTERS WITH LIPID BILAYERS: THERMOTROPIC CHANGES IN FLUORESCENCE POLARIZATION, PHASE TRANSITION AND CALCIUM IONOPHORESIS.

Deleers M, Defrise-Quertain F, Ruysschaert JM, Malaisse WJ
Lab. Experimental Medicine, Brussels Univ., 115 Bd de Waterloo, Brussels, Belgium
Res Commun Chem Pathol Pharmacol; 34(3):423-439 1981

The influence of phorbol esters upon the thermotropic behavior of multilamellar liposomes formed of dipalmitoylphosphatidylcholine (DPPC) or dimyristoylphosphatidylcholine (DMPC) was investigated, as a model for possible interferences of the phorbol esters with the phospholipid domain of biological membranes. Both biologically active (TPA, 12-O-tetradecanoylphorbol-13-acetate, PDD, phorbol-12,13-didecanoate) and inactive (4alpha-PDD, 4alpha-phorbol-12,13-didecanoate) phorbol esters lowered the temperature required to cause a fall in fluorescence polarization of a fluorescent probe inserted in the lipid matrix of the DMPC or DPPC liposomes and facilitated the process of calcium exchange-diffusion in DPPC liposomes containing the ionophore A23187. Both of these effect could be due to a decrease in viscosity of the liposomal matrix. However, differential scanning calorimetry revealed that the thermotropic changes evoked by each of these phorbol esters were not identical. In most cases, the phorbol esters decreased both the main phase transition temperature and enthalpy of melting. However, when TPA was incorporated in DMPC liposomes, ie when a myristoyl chain was present in both the phorbol ester and phospholipid, no change in the enthalpy of melting could be detected, whereas the main phase transition temperature decreased in proportion to the TPA content of the liposomes. These findings emphasize the view that phorbol esters indeed interact with phospholipids and that the characteristics of such an interaction may tightly depend on the precise chemical structure of both the phorbol ester and phospholipid under consideration. (Author abstract) (18 Refs)

17. EFFECT OF 12-O-TETRADECANOYL-PHORBOL-13-ACETATE ON CA2+ EFFLUX AND PROTEIN DISCHARGE IN PANCREATIC ACINI.

Gunther GR
Dept. Biochemistry, St. Jude Children's Res. Hosp., P. O. Box 318, Memphis, TN, 38101
J Biol Chem; 256(23):12040-12045 1981

When pancreatic acini are exposed to the peptide cerulein (an analogue of the hormone cholecystokinin) or the cholinergic agonist carbamylcholine, they exhibit a rapid release of intracellular Ca++ and a rise in the level of cGMP, accompanied by discharge of secretory proteins. The phorbol ester 12-O-tetradecanoyl-phorbol-13-acetate (TPA) stimulates protein discharge without affecting the level of cGMP, while N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) elevates cGMP, but does not el icit discharge. To clarify the relationships among these events, the effect of TPA and MNNG on Ca++ efflux in guinea pig acini was determined. Cells were incubated in medium containing 45Ca++ and transferred to medium

with nonradioactive Ca++ before adding the agents to be tested. Cerulein (10(-9) M), carbamylcholine (10(-5) M), and the Ca++ ionophore A23187 (5 ug/ml) all caused the release of 40-60% of the cell-associated 45Ca++ within 3 min. In contrast, acini incubated with 10(-7) M TPA, 10(-4) M MNNG, or no added agents retained over 80% of their 45Ca++ after 22 min. TPA caused significant secretory discharge within the first 15 min and did not block Ca++ efflux stimulated by other secretagogues. TPA-induced discharge requires energy and the presence of sufficient Ca++ in the extracellular medium. These observations are consistent with a model in which the rapid release of Ca++ into the cytoplasm triggers an increase in the level of cGMP and, by a separate series of events, protein discharge. TPA may act at a later point on the pathway to discharge, but before an obligatory step requiring Ca++. (Author abstract) (31 Refs)

REVIEWS AND OTHER RELATED STUDIES

18. NUTRITIONAL ASPECTS OF CANCER PREVENTION: AN OVERVIEW.

Silverman J
American Health Foundation, Naylor Dana Inst Disease Prevention, Valhalla, NY, 10595
J Am Vet Med Assoc; 179(12):1404-1409 1981

Human epidemiologic studies and supporting laboratory animal data on the relationship between nutrition and modification of cancer are reviewed. Carcinogenesis results from at least two steps: initiation and promotion. Diet, a major risk factor, can influence cancer in several ways. Food additives or contaminants can act as initiators, promoters, or inhibitors; nutritional deficiencies can cause biochemical changes. Nutritional excesses can cause metabolic changes which may then promote or inhibit cancer. A decrease in caloric intake leads to an increase in tumor latency and a decrease in the number of tumors. The incidence of breast cancer in humans is positively correlated with the consumption of animal protein, fat, and simple carbohydrates. Dietary fat also exerts a promotional effect on colonic cancer. Cancer of the prostate and pancreas is positively correlated with fat consumption, but the evidence is not absolute. Vitamin A apparently inhibits tumor formation during the promotional phase. Vitamin C does not manifest a clear protective effect against any cancer. Studies with selenium have produced disparate results, while nitrosamines have shown carcinogenicity in many species. In most cases nutrients modify rather than cause cancer. (100 Refs)

* U. S. GOVERNMENT PRINTING OFFICE : 1982—361-847/117

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Dept. Pathology, Univ. Toronto, 100 College St., Toronto, ON M5G 1L5, Canada
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Jorgensen NK, Cohr KH
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Scand J Work Environ Health; 7(3):157-168 1981

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Dept. Biochemistry, Univ. Surrey, Guildford, Surrey GU2 5XH, England
Food Cosmet Toxicol; 19(5):657-666 1981

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Suit H, Hall E, Frei E
Dept. Radiation Medicine, Massachusetts General Hosp., Boston, MA, 02114
Cancer Clin Trials; 4(Suppl):37-41 1981

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EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

8. ETIOLOGICAL CONCEPTS IN CERVICAL CARCINOGENESIS.
Kessler II
Dept. Epidemiology and Preventive Medicine, Univ. Maryland Sch. Medicine, 655 West Baltimore St., Baltimore, MD, 21201
Gynecol Oncol; 12(2,part2):S7-S24 1981

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Ugeskr Laeger; 143(42):2713-2716 1981
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Kalmaz EV, Kalmaz GD
Univ. Tennessee, Univ. Station 8163, Knoxville, TN, 37916
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13. CHEMICAL AND ENVIRONMENTAL AGENTS IN GASTROINTESTINAL CARCINOGENESIS.
Deschner EE, De Cose JJ, Sherlock P
Lab. Digestive Tract Carcinogenesis, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
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MODIFICATION OF CARCINOGENESIS

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Dept. Pathology, Massachusetts General Hosp., Boston, MA, 02114
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Honn KV, Bockman RS, Marnett LJ
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Gynecol Oncol; 12(2,part2):S25-S41 1981

18. VIRUS PAPILLOMAS IN HUMANS.
Nasemann T
Univ.-Hautklinik Eppendorf, Martinistr. 52, D-2000 Hamburg 20, W. Germany
Hautarzt; 32(11):601-606 1981
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MODIFICATION OF CARCINOGENESIS

SERIES CK04 No. 82/06 JUNE, 1982

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HE 20.3173/2:

MODIFICATION OF CARCINOGENESIS BY CHEMICAL AGENTS OR IRRADIATION

1. EFFECT OF PHENOBARBITAL, POLYCHLORINATED BIPHENYL AND SODIUM SACCHARIN ON HEPATIC AND RENAL CARCINOGENESIS IN UNILATERALLY NEPHRECTOMIZED RATS GIVEN N-ETHYL-N-HYDROXYETHYLNITROSAMINE ORALLY.

Hirose M, Shirai T, Tsuda H, Fukushima S, Ogiso T, Ito N

First Dept. Pathology, Nagoya City Univ. Medical Sch., 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467, Japan

Carcinogenesis; 2(12):1299-1302 1981

The effects of phenobarbital (PB), polychlorinated biphenyl (PCB) and sodium saccharin (SS) on hepatic and renal carcinogenesis induced by N-ethyl-N-hydroxyethylnitrosamine (EHEN) were examined in male F344 rats. The rats were given 0.1% EHEN in their drinking water for 2 wk and then diet containing 0.05% PB, 0.05% PCB or 5% SS for 32 wk. In wk 3, the right kidney was removed to promote renal neoplasia. The incidence of hepatocellular carcinoma was much higher in rats given PB or PCB than in controls given EHEN alone. PB administration significantly decreased the av number of renal-cell tumors per unit area and SS reduced the numbers of early neoplastic nodules. Treatment with PCB had no effect on renal carcinogenesis. These results indicate that chemicals may have either a promotive or inhibitory effect depending on the organ. (Author abstract) (25 Refs)

2. ENHANCING EFFECT OF BARBITAL ON N-2-FLUORENYL-ACETAMIDE INDUCED RAT LIVER LESIONS (MEETING ABSTRACT).

Tanaka T, Mori H, Nishikawa A, Takahashi M

Department of Pathology, Medical Gifu University, Gifu, Japan

Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Comparison of enhancing effects of phenobarbital (PB) and barbital (B) in hepatotumorigenesis was examined by quantitative analysis of the behavior of altered foci following discontinuation of N-2-fluorenylacetamide (FAA) administration. Thirty-four male ACI rats of 2 mo old were fed 0.02% FAA diet for 13 wk and some of them were sacrificed immediately. Remaining rats were divided into three groups and given a basal diet (Group I) or 0.05% PB diet (Group II) or 0.05% B diet (Group III) and sacrificed sequentially at 8 and 16 wk after the beginning of administration of each diet. The number of altered foci detected in hematoxylin and eosin or iron stain specimen/cm2 of the liver space at 16 wk of Group I remarkably decreased compared to that at termination of FAA feeding. However, the number of Group II or III was similarly maintained at 8 and 16 wk and the number at 16 wk of both groups was significantly higher than that of Group I. These data show that B like PB could be an enhancer in hepatotumorigenesis. (no Refs)

3. ENHANCEMENT OF HEPATOCARCINOGENESIS BY SEQUENTIAL ADMINISTRATION OF CHEMICALS; SUMMATION VERSUS PROMOTION EFFECTS (MEETING ABSTRACT).

Katayama S, Ohmori T, Williams GM

Department of Pathology, Osaka University Medical School, Osaka, Japan

Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

The enhancement of the effects of a carcinogen by a subsequently administered chemical is routinely regarded as evidence of promotion. On the other hand, as an extension of summation of mul tiple irreversible alterations produced by the total dose of a carcinogen, Nakahara and others have shown that sequential administration of two different carcinogens will produce a summation effect. Thus, the operational definition of a promoter based solely upon its enhancing effect in a protocol of sequential administration becomes questionable. To examine this problem, we undertook a comparison of the effects of phenobarbital (PB) versus diethylnitrosoamine (DEN) when each was given after 2-acetylaminofluorene (AAF). The effects of PB and DEN were comparable, however DEN exerted a greater enhancing effect on the oncogenic outcome of AAF exposure than PB. (no Refs)

4. INDUCTION OF RAT HEPATIC ORNITHINE DECARBOXYLASE BY THE TUMOR PROMOTERS 12-O-TETRADECANOYLPHORBOL-13-ACETATE AND PHENOBARBITAL IN VIVO; EFFECT OF RETINYL-ACETATE.

Bisschop A, Van Rooijen LA, Derks HJ, Van Wijk R

Lab. Carcinogenesis and Mutagenesis, Natl. Inst. Public Health, P.O. Box 1, 3720 BA Bilthoven, The Netherlands

Carcinogenesis; 2(12):1283-1287 1981

A single ip injection in rats of 20 ug 12-O-tetradecanoylphorbol-13-acetate (TPA) or 100 mg phenobarbital (PB)/kg body weight resulted in a transient increase in liver ornithine decarboxylase (ODC) activity. Maximal stimulation of ODC activity was observed approx 4 hr after application of TPA and 4-6 hr after treatment of PB. Six hr after TPA injection and greater than 8 hr after treatment with PB the ODC activity had returned to control level. ODC activity induction occurred in a dose dependent manner, maximal stimulation was obtained with 20-100 ug TPA and 100 mg PB/kg body weight, respectively. At higher doses the tumor promoters became increasingly inhibitory. The in vivo induction of rat liver ODC activity by TPA appeared to be under transcriptional control since administration of 2 mg actinomycin D/kg body weight or 50 mg cycloheximide/kg body weight 1 hr prior to application of the tumor promoter prevented the increase of ODC activity. Furthermore the TPA-stimulated ODC induction was shown to be very sensitive to retinyl-acetate (RA). An ip dose of RA of 0.2 ug/kg body weight applied 1 hr before TPA inhibited ODC induction by 35%. Increasing the dose of RA to 20 ug/kg body weight completely prevented the stimulation of ODC activity by TPA. (Author abstract) (43 Refs)

5. THE INFLUENCE OF CARCINOGEN TREATMENT ON CELL PROLIFERATION IN MOUSE COLONIC CRYPTS (MEETING ABSTRACT).

Kennedy MF, Tutton PJ, Barkla DH
Department of Anatomy, Monash University, Clayton, Australia
Clinical Oncology Society of Australia, November 24-17, 1981, Melbourne, Australia. The Society 70 pp., 1981.

The aims of the study were first, to observe the effect of treatment with the colonic carcinogen 1,2-dimethyl-hydrazine (DMH) on cell proliferation in mouse colon, and secondly to investigate the factors regulating proliferation in normal and DMH-treated colon. One-mo-old male mice were given weekly subcutaneous injections of DMH for 15 wk, and were then used in experiments within three wk of the final injection. Estimates of mitotic rates were obtained by a stathmokinetic technique, using vinblastine as the metaphase-arrest agent. The results show that DMH-treatment produced a significant increase in the rate of cell proliferation of colonic crypts. Cell proliferation was most rapid in the second lowest fifth of the crypt, whereas in DMH-treated animals the compartment of most rapid cell proliferation was elevated to the middle fifth of the crypt. The colonic crypts of both control and DMH-treated mice showed a reduction in mitotic rate following treatment with the alpha 2-adrenoceptor antagonist, Yohimbine. This reduction was equally distributed along the length of the crypts in both groups. The conclusions of the study are first, that DMH-treatment increases the mitotic rate in mouse colonic epithelium and also changes the site of most rapid cell proliferation to a higher level within the crypt. Secondly, it is apparent that at least one of the normal control mechanisms for regulating crypt cell proliferation in mouse colon, ie alpha 2 adrenoceptor-mediated inhibition, is maintained after DMH treatment. (no Refs)

6. PROMOTING EFFECTS OF HYDROGEN PEROXIDE UPON DUODENUM CARCINOGENESIS IN RATS (MEETING ABSTRACT).

Hirota N, Yokoyama T
Department of Pathology, Jichi Medical School, Tochigi, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

In an attempt to investigate the effect of hydrogen peroxide (HP) upon experimental duodenum carcinogenesis, male F344 rats were given ad libitum drinking water containing 1.5% HP for 4 wk prior to methylazoxymethanol acetate (MAM) (25 mg/kg) ip injection, 3 x, once every 2 wk. HP drinking was continuously given during the injection periods except as interrupted by 2-day intervals following each injection in which tap water was given. Then, one group of animals remained on the HP soln over the course of experiment, while HP drinking in another group was discontinued and switched to tap water for the remainder of the experiment. Duodenal carcinoma in the former group was found at 100% at 13 and 17 wk after the last injection, (8/8) and (10/10) respectively in contrast to 25% (2/8) and 30% (3/10) in the latter group given the same number of wk. In addition, when comparing the total number of carcinomas in each group, carcinogenesis in both duodenum and the upper portion of jejunum in the former group was more pronounced in effect. Treatment with MAM acetate alone induced lower incidence of duodenal carcinoma compared with combination treatment of MAM acetate and HP. Thus, prolonged oral administration of HP following the carcinogen injections to the rats conceivably played a distinct role in promoting duodenal carcinoma formation. (no Refs)

7. EFFECT OF PHENOBARBITAL ON CHEMICALLY-INDUCED NEOPLASMS, MALFORMATIONS AND DOMINANT LETHALS IN MICE (MEETING ABSTRACT).

Gotoh H, Nomura T, Shibata K, Hata S, Enomoto T, Kusafuka T, Miyamoto S, Sakamoto Y
Department of Fundamental Radiology, Osaka University School of Medicine, Osaka, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Phenobarbital (40-80 ug/g, sc) pretreatment of young adult and adult ICR/Jcl mice greatly diminished lung tumorigenesis initiated by urethane, furylfuramide (AF-2), and 7,12-dimethylbenz(a)anthracene (DMBA), while phenobarbital pretreatment enhanced embryo toxicities initiated by urethane, dimethyl-nitrosamine, 4-nitroquinoline-1-oxide, AF-2, and aminopyrine, but did not affect x-ray-induced ones. DMBA-induced dominant lethals were also enhanced by phenobarbital pretreatment. (no Refs)

8. SUPPRESSIVE EFFECT OF ALUMINIUM CHLORIDE ADMINISTRATION ON MOUSE LUNG CARCINOGENESIS BY DIMETHYLNITROSAMINE.

Yamane Y, Sakai K, Ohtawa M, Murata N, Yarita T, Ide G
Faculty Pharmaceutical Sciences, Chiba Univ., Yayoi-cho 1-33, Chiba 260, Japan
Gan; 72(6):992-996 1981

The compound dimethylnitrosamine was administered to mice by ip injection once a wk for 3 wk; a high incidence of lung tumor was found 6-8 mo after the final injection. In experiment I, the incidence of mice with lung tumors was 74%, and the av number of nodules per mouse was 15.6 within 6 mo after the final injection of dimethylnitrosamine. In mice given aluminum pretreatment, these values decreased to 65% and 6.7 (p less than 0.05), respectively. In experiment II, the incidence of mice with lung tumors was 100%, and the av number of nodules per mouse was 8.7 within 7.5 mo after the final injection of dimethylnitrosamine. In mice given aluminum pretreatment, these values decreased to 79% and 4.6 (p less than 0.05), respectively. (Author abstract) (19 Refs)

9. REDUCTION BY FUMARIC ACID OF CARCINOGENIC AND TOXIC EFFECTS OF 5-NITROFURAN NAPHTHYRIDINE DERIVATIVE (NFN) (MEETING ABSTRACT).

Kuroda K, Kanisawa M, Akao M
Chiba University, Chiba, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Feeding ICR mice with 0.012% NFN diet for 14 wk induced a high incidence of tumors ie squamous cell carcinomas and papillary adenomas of forestomachs in 3 and 9 of 12 mice, respectively, and papillary adenocarcinomas of lungs in all mice. Subsequent feeding with 1% fumaric acid diet reduced effectively the tumor incidence. No tumors developed in forestomachs of all 13 mice, and papillary adenocarcinomas of lungs in 6 of 13 mice. The ameliorating activity of fumaric acid against toxic effects of NFN were also shown in vitro in cultures of mouse and chick embryo cells. (no Refs)

10. EFFECT OF DISULFIRAM ON THE TOXICITY AND CARCINOGENICITY OF N-METHYL-N-NITROSOBENZYLAMINE IN RATS.

Schweinsberg F, Burkle V
Hygiene-Institut, Universitat Tubingen, Silchestr. 7, D-7400 Tubingen, W. Germany
J Cancer Res Clin Oncol; 102(1):43-47 1981

The concurrent application of disulfiram (710 mg/kg diet; or 200 mg/kg diet) effects a strong enhancement of the toxicity and an acceleration of the formation of esophageal tumors by N-methyl-N-nitrosobenzylamine (10 mg/l drinking water) in female SIV 50 rats. Besides that squamous cell papilloma in the trachea and extended squamous cell metaplasia in the bronchus system with potentially but not safely precancerous nature were seen. (Author abstract) (10 Refs) (In GER)

MODIFICATION OF CARCINOGENESIS BY DIETARY COMPONENTS OR DIGESTIVE FACTORS

11. EFFECTS OF DIETARY BRAN AND THE COLON CARCINOGEN 1,2-DIMETHYLHYDRAZINE ON A FECAL BETA-GLUCURONIDASE ACTIVITY IN MICE.

London JF, Clapp NK, Henke MA
Oak Ridge Graduate Sch. Biomedical Sciences, Univ. Tennessee, Oak Ridge, TN, 37830
Food Cosmet Toxicol; 19(6):707-711 1981

Daily variations in fecal beta-glucuronidase (BGLU) activity in BALB/c mice and variations in BGLU activity induced by different dietary brans and/or 1,2-dimethylhydrazine (DMH) were investigated. The effect of DMH on BGLU was significant. Three mo after DMH treatments, mice had persistently depressed BGLU activity compared to mice not treated with DMH. BGLU activities of animals on control or wheat bran diets were 4-5x higher than the activities in animals on either soya-bean bran or corn-bran diets and differed significantly from them. Animals fed the corn-bran diet consistently had the lowest BGLU activities in fecal stream. No synergistic action of any combination of variables was noted. (63 Refs)

12. EXPERIMENTAL COLON CARCINOGENESIS IS FACILITATED BY ENDOGENOUS FACTORS IN THE INTESTINAL CONTENTS.

Lewin MR, Ferulano GP, Cruse JP, Clark CG
Dept. Surgery, Univ. Coll. London, Rayne Inst., University St., London, WC1E 6JJ, England
Carcinogenesis; 2(12):1363-1366 1981

The theory that endogenous factors in the intestinal contents may be pathogenic during large bowel carcinogenesis was tested in the dimethylhydrazine (DMH)-induced rat colon cancer model. Thirty female Wistar rats, each serving as their own control, had a surgical transection of the proximal colon with reanastomosis to the rectum, therby excluding part of the colon from fecal contact. All rats then received a course of DMH (40 mg/kg body wt/wk sc for 10 weeks) while fed on Vivonex. This diet was selected because it lacks known exogenous (dietary) cocarcinogens. It also produces mucosal atrophy in functioning (proximal) colon, to parallel the disuse atrophy induced in the defunctioned (distal) colon. Animals remained on the diet throughout the experiment and were killed when moribund or at 40 weeks. At necropsy, the anatomical distribution, number, size and histological type of colon tumors were compared between functioning and defunctioned colonic segments within the same animal. At autopsy, there were significantly fewer colon tumors in the defunctioned segment (p less than 0.005). Furthermore, there were significantly fewer carcinomas (p less than 0.005) and fewer tumors greater than 1 cm diameter (p less than 0.01) in this segment. The data indicate that endogenous factors in the intestinal contents facilitate chemically-induced colon carcinogenesis. Luminal nutrition may be implicated. (Author abstract) (21 Refs)

13. INDUCTION OF RAT COLONIC EPITHELIAL ORNITHINE DECARBOXYLASE (ODC) BY BILE SALTS, AND ITS ENHANCEMENT BY COLON CARCINOGENS PRETREATMENT (MEETING ABSTRACT).

Takano S, Akagi M, Bryan GT
Department of Surgery, Kumamoto University, Kumamoto, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

A single intrarectal (ir) instillation of bile salts, presumptive colon promoters, results in a significant, early transient dose-response induction of rat colonic polyamine biosynthetic enzymes, ODC and S-adenosyl-L-methionine decarboxylase. Pretreatment by ir N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) or sc dimethylhydrazine (DMH) 1 wk before bile salt treatment enhanced and prolonged deoxycholate-induced ODC levels. This enhancement was dependent on pretreatment dose of MNNG, and was observed up to 3 mo after MNNG pretreatment. These data suggest that induced colonic ODC activity by bile salts may be related to colon carcinogenesis in a manner analogous to that shown to occur in mouse skin tumor systems. (no Refs)

14. MODIFICATION OF MAMMARY CARCINOGENESIS AND TISSUE PEROXIDATION BY SELENIUM DEFICIENCY AND DIETARY FAT.

Ip C
Dept. Breast Surgery and Breast Cancer Res. Unit, Roswell Park Memorial Inst., Buffalo, NY
Nutr Cancer; 2(3):136-142 1981

The independence of selenium (Se) and unsaturated fat intake as modifiers of the incidence of mammary tumors induced by 7,12-dimethylbenz(a)anthracene (DMBA) and the liability of mammary tissue to lipid peroxidation were studied. Female Sprague-Dawley rats were fed one of six synthetic diets (three different types of diets with and without Se supplementation) from weaning until termination of the experiment. The three basal diets contained different levels of tocopherol-stripped corn oil, 1%, 5%, and 25%. Mam mary tumors were induced by intragastric administration of a 5 mg dose of DMBA at 50 days of age. Measurement of Se-dependent glutathione peroxidase activity in the rat liver was used to determine the functional status of Se at 0, 10, 20, and 30 days after the rats were given either the basal Se-deficient diet or the supplemented regimen. In rats receiving an adequate supplement of Se (0.1 ppm) tumor incidence increased proportional to the amount of corn oil in the diet. A deficiency of Se in the diet resulted in a marked enhancement in tumor incidence and yield in rats fed the 25% corn oil regimen. Glutathione peroxidase activity in the mammary gland was not influenced by dietary fat but was severely depressed in the absence of added Se. Lipid peroxidation in the mammary tissue was elevated with increasing levels of dietary fat in rats supplemented with 0.1 ppm of Se. The unsupplemented 25% fat group showed signifi-

cant enhancement of tissue peroxidation when compared to their supplemented controls. Determination of peroxide in the synthetic diets demonstrated that corn oil when mixed with the other ingredients, auto-oxidized very quickly especially at room temperature. The amount of peroxide formed is proportional to the content of corn oil and to the length of storage. Se deprivation did not affect the tumor growth rate or the proliferation of malignant vs benign lesions. (40 Refs)

15. SIALIC ACID METABOLISM IN NUTRITIONALLY MODULATED MAMMARY GLAND CARCINOGENESIS.

Fox OF, Kishore GS, Carubelli R
Biomembrane Res. Lab., Oklahoma Medical Res. Foundation, 825 Northeast Thirteenth St., Oklahoma City, OK, 73104
Cell Mol Biol; 27(5):473-482 1981

The activities of CMP-N-acetylneuraminic acid synthetase, sialyltransferase and neuraminidase were investigated in female Sprague-Dawley rats with mammary adenocarcinomas induced by oral administration of 7,12-dimethylbenz[a]anthracene. The carcinogenic process was modulated by the levels and degree of unsaturation of the dietary lipids in the presence and in the absence of dietary antioxidants. The activities of the biosynthetic enzymes responsible for the activation and transfer of sialic acids, ie CMP-N-acetylneuraminic acid synthetase and sialyltransferase were higher in tumors than in control mammary glands. The cytosolic and membrane-bound neuraminidases, on the other hand, were higher in control tissue than in tumors. In the low-fat dietary group, which had the lowest rate of tumor incidence, a tocopherol effect on sialic acid metabolism was detected; rats fed low-fat diet supplemented with alpha-tocopherol exhibited the highest levels of control mammary gland sialyltransferase activity, whereas tocopherol deficiency was accompanied by a loss of the tumor-dependent enhancement of CMP-N-acetylneuraminic acid synthetase. The enzyme profiles in the livers of control and tumor-bearing rats, although less well defined, showed some of the general trends observed in mammary tissues. (Author abstract) (21 Refs)

16. STIMULATION OF DNA SYNTHESIS AND CELL PROLIFERATION IN THE LIVER OF RATS FED A CHOLINE-DEVOID DIET AND THEIR SUPPRESSION BY PHENOBARBITAL.

Abanobi SE, Lombardi B, Shinozuka H
Dept. Pathology, Univ. Pittsburgh Sch. Medicine, Pittsburgh, PA, 15261
Cancer Res; 42(2):412-415 1982

Feeding of a choline-devoid (CD) diet and dietary administration of phenobarbital (PHB) are efficient promoters of liver carcinogenesis in the rat. Furthermore, inclusion of PHB in a CD diet results in a synergistic effect, inasmuch as the promoting action of their combination is greater than the sum of those exerted by either agent alone. To investigate the mechanism(s) of action of the two promoters, liver DNA synthesis and liver cell proliferation were studied in rats fed a CD diet, a choline-supplmented diet, or the same diets to which 0.06% PHB was added. DNA synthesis was determined by [3H]thymidine incorporation into DNA and autoradiography, and cell proliferation was determined by mitosis counts. Feeding the CD diet caused an increase of both DNA synthesis and cell proliferation over those present in rats fed the choline-supplemented diet. Inclusion of PHB in the CD diet, on the other hand, inhibited DNA synthesis and cell proliferation. These results indicate that stimulation of cell proliferation per se may not be a sufficient condition for an agent to act as a promoter of liver carcinogenesis. (Author abstract) (32 Refs)

17. EFFECT OF VARIOUS ANTIOXIDANTS ON 7,12-DIMETHYLBENZ(A)ANTHRACENE INDUCED CARCINOGENESIS IN HAMSTERS.

Khadzhiolov DKh, Balanski RM
Inst. Oncology, Acad. Medical Sciences, Sofia, Bulgaria
Dokl Bolg Akad Nauk; 34(8):1189-1191 1981

Effect of antioxidants (AO) on the incidence of 7,12-dimethylbenz(a)anthracene (DMBA)-induced rhabdomyoblastomas was studied in Syrian hamsters. The animals received single im injection of DMBA (1 mg/kg); a mixture of AO (vitamin C, vitamin E, and sodium selenite) was given either 20 days before or 4 days after DMBA administration. By the end of the experiment (5 mo after DMBA injection), rhabdomyoblastomas were detected in 100% of the animals treated with DMBA alone and in 84.2% of the animals treated with DMBA + AO. (9 Refs) (In RUS)

18. CARCINOGENICITY EXAMINATION OF INFLORESCENCE OF ZINGIBER MIOGA ROSCOE (MEETING ABSTRACT).

Mori H, Kato K, Hirono I, Hosaka S, Aiso S
Department of Pathology, Gifu University, Gifu, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

The carcinogenicity of mioga was examined in ACI and Fisher 344 rats. In Experiment I, a test group of ACI rats received a diet containing mioga (1 part of mioga to 2 parts of basal diet) for 365 days. The experiment was terminated 480 days after the start of feeding. In Experiment II, a test group of Fisher 344 rats received the diet of mioga throughout the experiment of 639 days. Female ACI rats in Experiment I developed significantly more urinary bladder tumors than the control group. No carcinogenic activity was observed in males in Experiment I or males and females in Experiment II. Recently, the presence of L-arginine in a methanol extract of mioga and induction of bladder carcinomas in mice with implanted pellets containing L-arginine are reported. In this study, carcinogenicity of L-arginine and possible promoting effect on bladder carcinogenesis with N-Butyl-N-(4-hydroxy butyl)nitrosamine were also examined in ACI and Fisher rats by oral administration of 0.5% L-arginine soln. However neither carcinogenicity nor promoting effect was detected in both strains. (no Refs)

19. CARCINOGENICITY OF CARRAGEENAN.

Hopkins J
British Industrial Biological Res. Assoc.
Food Cosmet Toxicol; 19(6):779-781 1981

The carcinogenic potential of the food stabilizer carrageenan is discussed. Carrageenan has been identified as a cocarcinogen in studies with rats, enhancing methylnitrosourea-, azoxymethane- and dimethylhydrazine-induced colonic carcinoma. Carrageenan may also produce colonic carcinoma when used alone. (no Refs)

MODIFICATION OF CARCINOGENESIS BY HORMONAL OR GENETIC FACTORS

20. DEHYDROEPIANDROSTERONE: AN ANTI-OBESITY AND ANTI-CARCINOGENIC AGENT.

Schwartz AG, Hard GC, Pashko LL, Abou-Gharbia M, Swern D
Fels Res. Inst., Temple Univ., Philadelphia, PA, 19140
Nutr Cancer; 3(1):46-53 1981

Effects of long-term administration of dehydroepiandrosterone (DHEA) on female C3H-Avy/A (obese) and C3H-A/A (non-obese) mice were examined. DHEA treatment significantly inhibited wt gain in both strains of mice without suppressing food consumption. Food consumption of the DHEA-treated C3H-A/A mice was significantly greater than that of controls. DHEA significantly reduced the rate of breast cancer development. From 12 to 18 mo of age, the difference in breast cancer rates between controls and DHEA-treated C3H-A/A mice was significant. In the C3H-Avy/A mice, significant differences in breast cancer rates between controls and DHEA-treated mice were evident between 10 and 15 mo. The C3H-Avy/A control mice experienced a marked enhancement in rate of breast cancer development when compared to the C3H-A/A control group. A single ip injection of DHEA (15 mg/kg) inhibited 12-O-tetradecanoylphorbol-13-acetate (TPA) stimulation of 3H-thymidine incorporation in mouse epidermis. DHEA also blocked the TPA stimulation of 3H-thymidine incorporation in a rat kidney epithelial cell line; the inhibition was reversed by culturing for 20 hr in medium without DHEA. The results suggest that DHEA has an anti-carcinogenic effect and may have pharm acologic value in cancer prevention. (29 Refs)

21. HEPATOCARCINOGENICITY OF DIETHYLSTILBESTROL (DES) IN RATS (MEETING ABSTRACT).

Kamiya K, Seyama T, Kodama Y, Numoto M, Yokoro K
Department of Pathology, Hiroshima University, Hiroshima, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Despite the demonstration of carcinogenicity of DES in estrogen-susceptible tissues of some animal species, little is known about its carcinogenic effect in the liver. Castrated W/Fu rats treated with DES alone developed tumors of the liver (HT) in 30% of animals. By a combined treatment of DES and N-nitrosobutylurea (NBU) which is not hepatocarcinogen itself, HT incidence is much increased in several rat strains. In this system, androgen had no promotive effect in HT induction and the incidence correlated well with the dosage of DES. While castration prevents N-2-fluorenylacetamide (2-FAA) induced hepatocarcinogenesis, a combined treatment of 2-FAA and DES in castrated rats remarkably increased the incidence and tumor size of HT and shortened the latent period, suggesting the promotive effect of DES on the growth of transformed cells initiated by 2-FAA. Those results indicate that DES is a complete carcinogen with activities stronger in promotion than in initiation. (no Refs)

22. INFLUENCE OF PRENATAL EXPOSURE TO DIETHYLSTILBESTROL ON ESTROGEN AND PROGESTIN BINDING PROTEINS IN UTERI AND DIMETHYLBENZANTHRACENE-INDUCED MAMMARY TUMORS OF THE RAT.

Heidemann PH, Wittliff JL, Calhoon RE, Boylan ES
(c/o Wittliff) Dept. Biochemistry, Health Sciences Center, Louisville, KY, 40292
J Toxicol Environ Health; 8(4):667-686 1981

Various characteristics of steroid binding proteins from mammary tumors and from uteri of rats exposed prenatally to diethylstilbestrol (DES) were examined. Pregnant rats were treated with no hormone (group A) or with a total dose of 1.2 ug DES during the second (group B) or third (group C) trimester of gestation. Female offspring received 7,12-dimethylbenz(a)anthracene (DMBA) at day 50 +-1. Animals with large mammary tumors were subjected to bilateral ovariectomy. The experiment was terminated 7 mo after carcinogen treatment. High-affinity binding sites for (3H)estradiol-17beta and (3H)R5020 were found in all mammary tumors assayed. Estrogen receptor forms 8S and 4S were identified on sucrose gradients of low ionic strength regardless of prenatal treatment. Progestin receptors (PR) sedimenting at 4S were also identified in the tumors. PR form 7-8S was found only in tumors from intact animals. PR levels diminished after ovariectomy in mammary tumors and in uteri. Uterine progestin binding capacities and uterine wet wt did not decrease proportionally after ovariectomy in group C. PR capacities in mammary tumors from group C were higher than in other groups. Cytosol from mammary tumors in group C intact rats also had elevated PR levels. Uterine estrogen binding capacities did not vary significantly. Prenatal exposure to DES during the third trimester appeared related to persistent biochemical alterations in rat mammary tumors and uteri. Earlier exposure did not have the same effect. (61 Refs)

23. EFFECT OF BOLANDIOL DIPROPIONATE (ANABIOL), AN ANABOLIC HORMONE, ON DIETHYLNITROSAMINE-INDUCED HEPATOCARCINOGENESIS IN RATS.

Mochizuki Y, Sawada N, Furukawa K
Dept. Pathology, Cancer Res. Inst., Sapporo Medical Coll., Nishi-17-chome, Minami-1-jo, Chuo-ku, Sapporo 060, Japan
Gan; 72(6):969-973 1981

The effect of bolandiol dipropionate (Anabiol), an anabolic steroid hormone, on hepatocarcinogenesis was investigated in rats. Anabiol was injected at a dose of 5 mg into the thigh muscle at intervals of 2 wk, simultaneously with or subsequently to the 4-wk administration of diethylnitrosamine (DEN). The average number of tumors larger than 3 mm in diameter per rat in the subsequently treated group at 25 wk after commencement of DEN was significantly increased and the number of tumors larger than 5 mm in diameter per rat in the simultaneously treated group was significantly increased, when compared with that in the group given DEN alone. Thus, the enhancing effect of Anabiol on hepatocarcinogenesis was evident in terms of tumor size, regardless of whether the hormone was given simultaneously with or subsequently to the carcinogen. (Author abstract) (24 Refs)

24. SEX DIFFERENCE IN ENHANCEMENT OF GGTASE-POSITIVE FOCI BY HEXACHLOROBENZENE AND LINDANE IN RAT LIVER.

Pereira MA, Herren SL, Britt AL, Khoury MM
Health Effects Res. Lab., U. S. Environmental Protection Agency, Cincinnati, OH, 45268
Cancer Lett; 15(1):95-101 1982

The ability of hexachlorobenzene (HCB) and lindane (LN) in diethylnitrosamine (DENA) pretreated rats to enhance the incidence of gamma-glutamyltranspeptidase (GGTase)-positive foci was determined. Male and female Sprague-Dawley rats (175-225 g) were used in the experiments. HCB and LN increased the incidence of DENA and initiated GGTase-positive foci in rat liver. Animals that received a partial hepatectomy or sham operation, and then were given HCB or LN in their diet, developed relatively few GGTase-positive foci. When DENA was administered 24 hr after the partial hepatectomy, as compared to the sham operation, there was a slightly increased incidence of GGTase-positive foci. In female rats that received either a partial hepatectomy or sham operation followed by DENA, HCB and LN increased the incidence of GGTase-positive foci. In male rats, HCB and LN increased the incidence of GGtase-positive foci only when a partial hepatectomy preceded the DENA. The enhancement of GGtase-positive foci by HCB and LN was greater in female, com pared to male rats. The results suggest that hepatocarcinogenicity of HCB and LN results in tumor promotion. (33 Refs)

25. EFFECT OF MAJOR HISTOCOMPATIBILITY GENE COMPLEX (MHC) ON THE SUSCEPTIBILITY TO URETHANE INDUCED LUNG TUMORS IN MICE (MEETING ABSTRACT).

Moriwaki K, Miyashita N
Department of Cytogenetics, National Institute of Genetics, Mishima, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

In addition to a pulmonary tumor resistance (ptr) gene probably located on chromosome 11, MHC seems to function in the processes of tumorigenesis. This study aims to reveal the effect of MHC on urethane-induced lung tumor incidence. In susceptible A/J mouse, av foci of lung tumor is 28.0. If H-2a complex of A/J is replaced by H-2b or H-2s, tumor foci reduce to about 10. These results clearly showed the profound regulatory function of MHC for the lung tumor development by urethane in mouse strains with susceptible ptr gene. Suppressive effect of wild-derived chromosomes is also investigated. (no Refs)

MODIFICATION OF CARCINOGENESIS BY VIRUSES, BACTERIA OR IMMUNE SYSTEM COMPONENTS

26. THE EFFECT OF ADJUVANT IMMUNOTHERAPY ON TUMOR RECURRENCE AFTER SEGMENTAL RESECTION OF CARCINOGEN-INDUCED WISTAR/FURTH PRIMARY BOWEL ADENOCARCINOMAS.

Steele G, Harte PJ, Rayner AA, Corson JM, Madara J, Munroe AE, King VP, Wilson RE
Brigham and Women's Hosp., 75 Francis St., Boston, MA, 02115
J Immunol; 128(1):7-10 1982

Primary bowel tumors were induced in Wistar/Furth (W/Fu) rats by 16 weekly sc injections of 1,2-dimethylhydrazine (DMH). After 'curative' resection of primary adenocarcinomas of the colon, 75% of control rats who received no further treatment developed local or regional recurrence within 22 wk. In four separate experiments, rats immunized after primary tumor resection by three weekly sc inoculations of 1 x 10(6) irradiated (10,000 rad) DMH-W15 sarcoma cells (no tumor-associated antigens cross-reacting with bowel adenocarcinomas) developed recurrent tumor at a rate similar to the controls. By contrast, after primary bowel tumor resection, rats immunized with DMH-W163 colon adenocarcinoma (possessing tumor-associated antigens cross-reactive with other W/Fu bowel adenocarcinomas) showed a consistently reduced rate of local or regional recurrence compared to either of the controls (chi2 = 4.62, p less than 0.05) or the rats immunized with sarcomas (chi2 = 5.42, p less than 0.05). By 22 wk after primary tumor resection, only 35% of the DMH-W163-immunized animals in each of the four experiments showed recurrence. No deaths from recurrences were noted in any of the experimental groups after this time, and selected animals sacrificed in the immunized groups up to 30 wk after primary tumor resection were documented to be disease-f ree. Protection against tumor recurrence was, therefore, a reflection of increased disease-free survival. No change in the effectiveness of immunoprotection in this model could be demonstrated after resection of less invasive primary tumors. These data reflect the utility of a new model in which modification of the natural history of individual primary bowel adenocarcinomas can be examined. The similarities and differences between this system and humans with colon cancer are discussed. (Author abstract) (13 Refs)

OTHER STUDIES OF THE MODIFICATION OF CARCINOGENESIS

27. APPLICATION OF QUANTITATIVE STEREOLOGY TO THE EVALUATION OF ENZYME-ALTERED FOCI IN RAT LIVER.

Campbell HA, Pitot HC, Potter VR, Laishes BA
(c/o Pitot) McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI, 53706
Cancer Res; 42(2):465-472 1982

The mathematical science of quantitative stereology has established relationships for the quantitation of elements in three-dimensional space from observations on two-dimensional planes. This report describes the utilization and importance of such mathematical relationships for the quantitative analysis of focal hepatic lesions in terms relative to the vol of the liver. Three examples are utilized to demonstrate the utility of such calculations in the three-dimensional quantitation of hepatic focal lesions. The first is that of a computer-simulated experiment based on defined hypothetical situations. The simulations demonstrate the applicability of the computations described in this report to the evaluation of two-dimensional data from typical animal experiments. The other two examples are taken from actual experiments and involve the transplantation of hepatic cell populations into the liver of suitably prepared hosts and the quantitation of altered foci produced by initiation with diethylnitrosamine-partial hepatectomy followed by promotion with phenobarbital. These studies clearly demonstrate that the frequency and size of foci intersections viewed on two-dimensional tissue sections do not necessarily reflect the number or size of foci in the three-dimensional tissue. Only by quantitating the number and size of the foci in relation to the three-di-

mensional vol of the tissue can one determine the validity of the proportionality of data from two-dimensional measuremenis to the total number of foci per volume of tissue. Such a conclusion has important implications for quantitative studies on hepatocarcinogenesis as well as for the enumeration of premalignant lesions which occur during the natural history of carcinogenesis in any solid tissue. (29 Refs)

28. ENHANCING EFFECT OF URINE ON BLADDER CARCINOGENESIS BY MNU (MEETING ABSTRACT).

Miyata Y, Babaya K, Oyasu R
Department of Pathology, Northwestern University Medical School, Chicago, IL
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 198 1, Sapporo, Japan. The Association 415 pp., 1981.

It has been firmly established that urine plays an important role in urinary bladder carcinogenesis. Using a heterotopically transplanted rat bladder (HTB), we have demonstrated that normal urine has a tumor enhancing effect on bladder carcinogenesis. In that study, however, the bladder epithelium was exposed to carcinogen in the presence of urine, and possible involvement of urine in the initiation step could not be ruled out. The present investigation was conducted with 2 major goals in mind: 1) to remove the possible effect of urine during the initiation step, and 2) to establish a model system where potential modifiers of bladder carcinogenesis may be tested. Young male Fisher rats, 4 wk post transplant, were divided into 6 groups. For the first 2 groups, 0.25 mg of methyl-1-nitrosourea (MNU) was instilled directly into HTB once a wk 3 x. A wk after the last dose, one half of rats received normal rat urine into HTB (group 1), and the other half 0.9% saline (group 2) weekly. The second 2 groups of rats received a single dose of MNU, and subsequently urine (group 3) or saline (group 4). Groups 5 and 6 rats served respectively as urine and saline controls without prior exposure to carcinogen. The bladder cancer incidences in HTB's are as follows: group 1, 16/18; group 2, 6/18; group 3, 14/23; group 4, 2/22; group 5, 1/19; and group 6, 0/18. The results indicate urine plays an enhancing role in the bladder where epithelial cells are initiated by carcinogen in the urine-free environment. The schedules established above may be useful to test the role of modifiers of carcinogenesis. (1 Ref)

29. ENHANCING EFFECT OF VAGOTOMY AND PYLOROPLASTY ON GASTRO-INTESTINAL NITROSAMIDE-INDUCED CARCINOGENESIS IN HAMSTERS (MEETING ABSTRACT).

Mori H, Domellof L, Weisburger JH, Williams GM
Department of Pathology, Gifu University, Gifu, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

The possible promoting effect of vagotomy and pyloroplasty on N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) induced carcinogenesis in the gastrointestinal (GI) tract was studied in Syrian golden hamsters on a high fat diet. After truncal vagotomy and pyloroplasty (Group 1) or sham operation (Group 3), 50 ug/ml of MNNG was given for 4 mo in drinking water. Similarly operated (vagotomy + pylorplasty) (Group 2) or non-operated (Group 4) animals without carcinogen administration served as controls. Spindle cell sarcomas of the stomach and small intestine as well as spindle cell proliferation occurred frequently in the MNNG treated hamsters (Groups 1 and 3). A small number of hamsters in Group 1 also developed adenocarcinomas and rosette-forming tumors in GI tracts. Statistically, a significantly higher incidence of tumors o f the GI tract or glandular stomach was noted in Group 1 compared to Group. The results suggest that this operation has an enhancing effect on the MNNG carcinogenicity in the hamster. (no Refs)

30. THE SIGNIFICANCE OF A PHYSICAL FACTOR FOR TUMORGENESIS IN RAT INTESTINE (MEETING ABSTRACT).

Shindo K, Kotobuki T, Miyamoto T, Kosaki G
2nd Department of Surgery, Osaka University, School of Medicine, Osaka, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

The aim of this work is to investigate the influence of stenosis or continuous spasm on intestinal tumorigenesis. One hundred Sprague-Dawley rats were laparotomized and a stenosis was made by a ligature put around the cecum, colon and rectum. Ten mo later the intestine was observed. Eighty-five rats tolerated the experiment and revealed the following histologic lesions: Hyperplastic polyp; Mucosal atypia; Mucosal cyst; Polypoid fold; Lymphoid hyperplasia; and Submucosal lipoma. Various kinds of tumors were made without chemical carcinogen. Intestinal stenosis or spasm promotes tumor formation. (no Refs)

31. ENHANCED INHIBITION OF MAMMARY CARCINOGENESIS BY COMBINED TREATMENT WITH N-(4-HYDROXYPHENYL)RETINAMIDE AND OVARIECTOMY.

McCormick DL, Mehta RG, Thompson CA, Dinger N, Caldwell JA, Moon RC
Lab. Pathophysiology, Life Sciences Div., IIT Res. Inst., Chicgo, IL, 60616
Cancer Res; 42(2):508-512 1982

Bilateral ovariectomy and dietary administration of the retinoid N-(4-hydroxyphenyl)retinamide (4-HPR) are both effective inhibitors of chemical carcinogenesis in the rat mammary gland. The present study was designed to determine whether an enhanced inhibitory effect is obtained with combined ovariectomy and 4-HPR administration, compared to either treatment alone. In separate experiments, 50-day-old virgin female Sprague-Dawley rats received either a single iv injection of 50 mg N-methyl-N-nitrosourea per kg body wt or a single intragastric dose of 20 mg 7,12-dimethylbenz(a)anthracene. The experimental design was the same in both the N-methyl-N-nitrosourea and 7,12-dimethylbenz(a)anthracene experiments: Group 1, 25 intact rats, placebo diet; Group 2, 25 intact rats, supplement of 782 mg 4-HPR per kg diet; Group 3, 50 ovariectomized rats, placebo diet; Group 4, 50 ovariectomized rats, supplement of 782 mg 4-HPR per kg diet. Feeding of the 4-HPR supplement was begun 7 days after carcinogen administration; ovariectomy was performed 7 days post-7,12-dimethylbenz(a)anthracene or 14 days post-N-methyl-N-nitrosourea. In both experiments, combined ovariectomy plus 4-HPR was significantly more active in suppressing mammary cancer induction than was either manipulation alone. 4-HPR was a more effective inhibitor of carcinogenesis in ov ariectomized rats than in intact animals. These data indicate that 4-HPR is highly effective in inhibiting ovarian hormone-independent cancers and suggest that retinoid inhibition of mammary carcinogenesis does not involve an influence on ovarian hormone action. (Author abstract) (19 Refs)

32. CYTOGENETICS OF MURINE THYMIC LYMPHOMAS INDUCED BY N-METHYL-N-NITROSOUREA: DIFFERENCE IN INCIDENCE OF TRISOMY 15 IN THYMIC LYMPHOMAS INDUCED IN NEONATAL AND ADULT MICE.

Chan FP, Ens B, Frei JV
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Cancer Genet Cytogenet; 4(4):337-344 1981

Chromosome complements of murine thymic lymphomas induced by an alkylating agent N-methyl-N-nitrosourea (MNUA) were analyzed microscopically and karyotypically using the Q-banding technique. The chemical carcinogen was injected intraperitoneally into either neonatal or 7-wk-old CFW/D mice. In addition, thymic lymphomas induced in 7-wk-old AKR mice and thymic lymphomas developed spontaneously in this strain were also examined. All six lymphomas induced in neonatal CFW/D had hyperdiploid cell lines that accounted for 90% of the cells analyzed. Chromosome analysis of lymphomas induced in adult CFW/D mice showed that only four out of nine lymphomas had predominantly hyperdiploid cell lines. The remaining five lymphomas had diploid modal chromosome number although they also carried a variant line characterized by 41 chromosomes. All eight lymphomas induced in adult AKR mice and six out of seven spontaneous AKR lymphomas showed predominantly diploid modal line. The remaining spontaneous lymphoma had a hyperdiploid stem line of 41 chromosomes. Microscopic and karyotypic analysis further identified trisomy 15 as the regular chromosome abnormality in the hyperdiploid cells in lymphomas of each group, whereas cells with diploid chromosome number had no detectable chromosome abnormality. Additional trisomies were also found, but their appearance was restricted to individual tumors. Thus, the incidence of trisomy 15 in lymphomas induced by MNUA in adult CFW/D and AKR mice, as well as in the spontaneous AKR lymphomas, is significantly lower than that in lymphomas induced in neonatal mice by the same carcinogen. (Author abstract) (19 Refs)

STUDIES OF TUMOR PROMOTION OR COCARCINOGENESIS IN MOUSE SKIN

33. SENSITIVITY TO TWO-STAGE CARCINOGENESIS OF SENCAR MOUSE SKIN GRAFTED TO NUDE MICE.

Yuspa SH, Spangler EF, Donahoe R, Ferguson SG, Wenk M, Hennings H
Lab. Experimental Pathology, NCI, Bethesda, MD, 20205
Cancer Res; 42(2):437-439 1982

SENCAR mice are extremely susceptible to two-stage skin carcinogenesis, while BALB/c mice are relatively resistant. Skin grafts to BALB/c nude mice were performed with full-thickness skin from SENCAR and BALB/c donors, and tumor formation was monitored in grafted skin, surrounding host skin , and intact SENCAR, BALB/c and nude mice. Initiation was accomplished by exposure to 20 ug dimethylbenz(a)anthracene and promotion by repeated exposure to 12-O-tetradecanoylphorbol-13-acetate. SENCAR skin retained a high sensitivity to carcinogenesis when grafted to nude hosts, whereas BALB/c skin remained resistant. The donor type did not influence the tumor yield in surrounding nude host skin. The rate of tumor regression was not altered in SENCAR skin grafts on nude mice relative to intact SENCAR skin. These results indicate that the unusual sensitivity of SENCAR epidermis to chemical carcinogenesis is not due to altered systemic factors but is a property of the skin itself. (Author abstract) (11 Refs)

34. SKIN TUMOR PROMOTION BY PHORBOL ESTERS IS A TWO-STAGE PROCESS.

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Proc Natl Acad Sci USA; 78(12):7722-7726 1981

In the semisynthetic compound phorbol 12-retinoate 13-acetate (PRA), the antipromoting principle of vitamin A acid is combined with the structure of a phorbol ester tumor promoter. In skin of NMRI mice, a single topical application of PRA induces skin inflammation, epidermal proliferation, and sustained hyperplasia to a similar extent and apparently along the same pathway as an equimolar dose of the strong tumor promoter phorbol 12-myristate 13-acetate (PMA). The mitogenic effects of both PRA and PMA are mediated by prostaglandin E synthesis. However, in mouse skin initiated with 7,12-dimethylbenz[a]anthracene, PRA does not promote tumor development, even at a high dose. Under continuous PRA treatment, however, one to four applications of PMA (insufficient by itself to promote tumor growth) gave a strong tumor response. Thus, it can be demonstrated that the effects necessary for tumor promotion can be brought about by a single application of PMA and that the subsequent chronic hyperproliferation of epidermis is probably necessary only to make the tumors visible. By using the nonpromoting irritant mitogen PRA, the concept of two-stage tumor promotion can thus be strongly supported. Furthermore, in the NMRI mouse, PRA is a much more potent second-stage promoter than mezerein, recently reported to be an incomplete promoter in the Sencar mouse. (Author abstract) (23 Refs)

35. THE TIME NEEDED FOR NORMALIZATION OF HAIRLESS MOUSE EPIDERMIS AFTER TREATMENT WITH TWICE WEEKLY TOPICAL SKIN APPLICATIONS OF 10 NMOL 12-O-TETRADECANOYLPHORBOL-13-ACETATE IN ACETONE, OR ACETONE ALONE, FOR 18 WEEKS. A MORPHOLOGIC AND CELL KINETIC STUDY.

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Inst. Pathology, Univ. Oslo, Rikshospitalet, Oslo 1, Norway
Carcinogenesis; 2(12):1353-1358 1981

In order to find the time needed for normalization of the mouse epidermis after an 18 wk-course of treatment according to the two-stage carcinogenesis protocol, hairless mice were treated with 10 nmol 12-O-tetradecanoylphorbol-13-acetate in 100 ul reagent grade acetone twice weekly for 18 wk. A control group was treated similarly with 100 ul reagent grade acetone alone. Groups of four animals were killed each wk for 10 wk thereafter, and morphologic and cell kinetic studies performed. To assess hyperplasia, the number of basal and suprabasal cells per unit length of epidermis was counted. The mitotic rate was determined by a stathmokinetic method using Colcemid for arrest of mitoses. DNA synthesis was measured by determining the labeling index and the DNA-specific activity after injection of [3H]thymidine. Flow cytometric measurements were performed to find the fraction of cells in the various cell cycle phases at each observation point. Treatment with acetone alone led to a moderate hyperplasia and a slight increase in the mitotic rate, which persisted during the 10 wk of subsequent observation. Treatment with TPA led to a considerable hyperplasia which first increased for 3 wk and then

decreased, and was still significant 10 wk after termination of treatment. The line of best fit through the values indicated that a time of about 20 wk may be needed before normal epidermal thickness is reestablished. TPA treatment also led to a pronounced increase in the labeling index and a high mitotic rate. These variables became almost normal after approx 8-10 wk, but one cannot know whether one or more new waves of proliferation take place more than 10 wk after termination of TPA treatment. If a proper 'inverse' experiment according to the two-stage theory of carcinogenesis should be performed, one had to wait at least 20 wk after termination of promotion before the initiating dose of carcinogen should be applied. The possibility of increased acquired resistance to carcinogens during promotion is also discussed. (Author abstract) (10 Refs)

36. TUMOR PROMOTING AND SKIN IRRITANT DITERPENE ESTERS OF EUPHORBIA VIRGATA LATEX.

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Neoplasma; 28(5):555-558 1981

The mouse ear irritant latex of Euphorbia virgata has been found to contain various skin irritant and non-irritant esters of the diterpene ingenol. In cocarcinogenic assay on dorsal back skin of NMRI mice, acetone extract of this latex produces squamous cell papilloma. Using a combination of biologic and chemical separation techniques, one of the initiator-promoters for skin carcinogenesis has been identified as 3-0-2-methyl-decanoyl ingenol. (Author abstract) (14 Refs)

37. CHEMICAL CARCINOGENESIS BY THE TWO-STAGE PROTOCOL IN THE SKIN OF MASTOMYS NATALENSIS (MURIDAE) USING TOPICAL INITIATION WITH 7,12-DIMETHYLBENZ(A)ANTHRACENE AND TOPICAL PROMOTION WITH 12-O-TETRADECANOYLPHORBOL-13-ACETATE.

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Virchows Arch [Cell Pathol]; 38(1):13-21 1981

The long-term (34 wk) topical administration of 7,12-dimethylbenz(a)anthracene (DMBA) to the skin of male and female Mastomys induced a broad spectrum of benign and malignant tumors in all animals treated. In a two-stage carcinogenesis experiment with topical initiation with DMBA and topical promotion with 12-O-tetradecanoylphorbol-13-acetate (TPA), 50% of the animals developed both benign and malignant skin tumors. In general, benign tumors occurred between wk 15 and 25, whereas malignant tumors were seen 40 wk after initiation. In contrast to the situation in Mus musculus, the benign tumors consisted mainly of keratoacanthomas instead of fibroepitheliomas. In the non-initiated, TPA-treated, control group four benign and four malignant tumors were seen, whereas animals of the DMBA-initiated, acetone-treated control group were free of tumors. The promotion of virus transformed cells with TPA is discussed. (Author abstract) (36 Refs)

38. EFFECT OF LAMBDA CARRAGEENAN ON TUMOR FORMATION IN TWO STAGE CHEMICAL CARCINOGENESIS OF MOUSE SKIN (MEETING ABSTRACT).

Inoue T, Yoshimoto T, Shindo H, Ogura T, Hirao F, Yamamura Y
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Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

The dorsal skins of C57BL/6 male mice were initiated by 20 ug dimethylbenzanthracene (DMBA) at eleven wk old. Seven wk later, they were promoted by 2.5 ug 12-O-tetradecanoylphorbol-13-acetate (TPA) twice weekly for 30 wk. One mg lambda-carrageenan was injected ip three x for a wk before initiation (group 1), before the beginning of promotion (group 2), or at the 7th wk of promotion (group 3). Mice in group 4 were not treated with lambda-carrageenan. The incidence of papilloma and the mean number of papillomas per mouse were reduced by lambda-carrageenan treatment. (no Refs)

39. PHORBOL-12,13-DIESTER 12-ESTER HYDROLASE MAY PREVENT TUMOUR PROMOTION BY PHORBOL DIESTERS IN SKIN.

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Nature; 295(5845):152-154 1982

The relationship between skin phorbol-12,13-diester 12-ester hydrolase (PDEH) level and species susceptibility to 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced skin tumor promotion was studied. Enzyme activity was determined by incubating tissue extracts with 3H-phorbol-12,13-dibutyrate (3H-PDBu) for 30 min and measuring the amount of remaining 3H-PBDu by its binding to mouse brain membrane fractions (phorbol ester receptors). PDEH activity was absent in mouse skin but present at high levels in hamster, rat, guinea pig, and rabbit skin. Skin from all species contained TPA receptors, indicating that lack of responsiveness to TPA is not due to absence of specific TPA receptors. Extracts from hamster, rat, guinea pig and rabbit skin reduced 3H-PDBu receptor binding and converted the compound to biologically inactive phorbol-13-butyrate. Extracts from mouse, cat, dog, monkey, or human skin did not affect the binding or metabolism of 3H-PBDu. The results demonstrate that PDEH can inhibit tumor promotion by inactivating TPA and other active phorbol esters; active phorbol esters may act as tumor promoters in cat, dog, monkey, and human skin. (27 Refs)

CELL CULTURE STUDIES OF MECHANISMS

40. ENHANCED TRANSFORMATION OF MOUSE 10T1/2 CELLS BY 12-O-TETRADECANOYLPHORBOL-13-ACETATE FOLLOWING EXPOSURE TO X-RAYS OR TO FISSION-SPECTRUM NEUTRONS.

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Cancer Res; 42(2):477-483 1982

Addition of the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) to C3H/10T1/2 cells after exposure to either x-rays or to fission-spectrum neutrons increases significantly the frequency of transformation without any effect on cell survival. However, treatment of unirradiated cells with 0.1 ug of TPA per ml alone results in a small increase in transformation frequency above background (ie, from 1.1 x 10(-5) to 1.0 x 10(-4)). Thus, besides being a promoter, TPA is also a weak initiator. Enhancement of radiation-induced transformation by TPA was relatively greater after low compared to high doses of either radiation. In addition, TPA causes the relative biological effectiveness of neutrons compared to x-rays to increase with increasing dose or with increasing frequency of transformation rather than to decrease, when TPA is not used. For x-ray doses from zero to approx 120 rads, TPA raises transformation to frequencies approx equal to those due to neutrons alone. Analysis of TPA enhancement in the context of the combined effect of two inducing agents, ie, TPA plus a radiation, indicates that with either radiation TPA acts synergistically. Lastly, TPA was found to alter the dependence of transformation frequency on the density of viable cells. As opposed to a constant frequency of transformants per surviving (or viable) cell, which we observed after a fixed dose of x-rays or neutrons for a range of cell inocula the addition of TPA increased the frequency of transformation for all cell inocula (ie, from approx 20 to 6,000 viable cells per 90-mm Petri dish). However, the frequency of transformation decreases with increasing size of the inoculum, a result that we interpret to indicate the combined effect of an interference with cell-to-cell communication by TPA plus the fading of initiation events due to the radiation. (Author abstract) (41 Refs)

41. EQUIVALENCY OF ENDOTHELIAL CELL GROWTH SUPPLEMENT TO IRRADIATED FEEDER CELLS IN CARCINOGEN-INDUCED MORPHOLOGIC TRANSFORMATION OF SYRIAN HAMSTER EMBRYO CELLS.

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Lab. Biology, Div. Cancer Cause and Prevention, NCI, Bethesda, MD, 20205
JNCI; 68(1):127-131 1982

Endothelial cell growth supplement (ECGS), an extract of bovine neural tissue with growth-promoting properties for human endothelial and epithelial cells and for mouse BALB/c fibroblast-like cells, can be substituted for feeder cells in a quantitative 7-day Syrian hamster embryo cell colony in vitro model of carcinogenesis. Inclusion of 50 or 100 ug ECGS/ml medium throughout the 7-day growth period produced results equal to those obtained with feeder cells. The frequency and morphology of normal fibroblast colonies and carcinogen-induced morphologically transformed cell colony growth in the presence of ECGS were similar to those in the presence of feeder cells. A positive dose-response relationship in transformation by benzo[a]pyrene occurred. The frequency of transformed colonies following UV irradiation and treatment of the cells with the cocarcinogenic tumor promoter 12-O-tetradecanoylphorbol 13-acetate was greatly augmented, and lymphotoxin, a lymphokine with anticarcinogenic activity, reduced transformation. Thus ECGS can substitute for feeder cells in supporting in vitro transformation and eliminates a potential complex source of variability for studies where interaction(s) with feeder cells are a consideration. The mechanics of this model system was simplified, and its versatility for the study of physiologic, carcinogenic, and other pathophysiologic processes was broadened. (Author abstract) (19 Refs)

42. ANTIPAIN AND RADIATION EFFECTS ON ONCOGENIC TRANSFORMATION AND SISTER CHROMATID EXCHANGES IN SYRIAN HAMSTER EMBRYO AND MOUSE C3H/10T1/2 CELLS.

Geard CR, Rutledge-Freeman M, Miller RC, Borek C
Radiological Res. Lab., Dept. Radiology, Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032
Carcinogenesis; 2(12):1229-1233 1981

Depending on its time of addition to Syrian hamster embryo or mouse C3H 10T1/2 cells the protease inhibitor antipain (AP) can enhance, or reduce, radiation induced-oncogenic transformations. These opposing influences are not paralleled by changes in sister chromatid exchanges in either cell system. A 24 hr treatment with 10 uM AP prior to, and during irradiation, with removal 10 min after irradiation results in greater than a two-fold increase in transformants. Conversely, a 24 hr treatment beginning 10 min after irradiation results in about a two-fold decrease in transformants. The utility of AP as an agent for the reduction of tumorigenesis is brought into question, since quite short temporal differences in application can result in near five-fold differences in the frequencies of oncogenic transformations. (Author abstract) (32 Refs)

43. INITIATOR AND PROMOTER INDUCED SPECIFIC CHANGES IN EPIDERMAL FUNCTION AND BIOLOGICAL POTENTIAL.

Yuspa SH, Hennings H, Lichti U
Lab. Cellular Carcinogenesis and Tumor Promotion, Div. Cancer Cause and Prevention, NCI, Bethesda, MD, 20205
J Supramol Struct Cell Biochem; 17(3):245-257 1981

Cellular changes involved in multistage carcinogenesis were studied. Epidermal cells were isolated from BALB/c or SENCAR newborn and adult mice. Mouse epidermal basal cells can be selectively cultivated in medium with a Ca concentration of 0.02-0.09 milliM (mM). Terminal differentiation and sloughing of mature keratinocytes occur when the Ca concentration is increased to 1.2-1.4 mM. Basal cellsderived from mouse skin initiated in vivo yield foci that resist terminal differentiation. The induction of the enzyme ornithine decarboxylase (ODC) was used as marker for responsiveness to phorbol esters. ODC induction after exposure to 12-O-tetradecanoylphorbol-13-acetate (TPA) in basal cells was enhanced 20x over the response of a culture population containing both differentiating and basal cells. When basal cells were induced to differentiate by increased Ca, responsivness was lost within several hr. ODC was max at 3 hr after exposure to low concentrations of TPA or to weak promoters of the phorbol esters series. ODC max was at 9 hr with higher concentrations of TPA. Remaining basal cells proliferated and became resistant to induced differentiation by 1.2 mM Ca when differentiated cells were sloughed from the dish. Data provide additional evidence of basal cell heterogeneity in which TPA induces one subpopulation to differentiate while another is stimulated to

proliferate and resist a differentiation signal. Tumor promoters would cause redistribution of subpopulations of epidermal cells in skin by their ability to produce heterogeneous responses. (54 Refs)

44. THE TUMOR PROMOTER, 12-O-TETRADECANOYLPHORBOL-13-ACETATE ACCELERATES KERATINOCYTE DIFFERENTIATION AND STIMULATES GROWTH OF AN UNIDENTIFIED CELL TYPE IN CULTURED HUMAN EPIDERMIS.

Hawley-Nelson P, Stanley JR, Schmidt J, Gullino M, Yuspa SH
Lab. Experimental Pathology, Div. Cancer Cause and Prevention, NCI, Bethesda, MD, 20205
Exp Cell Res; 137(1):155-167 1982

Studies were conducted to determine the effects of the mouse skin tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) on cultured human epidermal cells for comparison with known effects on mouse keratinocytes. In contrast to its effect on mouse cells, TPA did not stimulate human epidermal cell DNA synthesis. TPA stimulated differentiation in human keratinocy tes resulting in sloughing of many cells by the 3rd day after exposure. Quantitative assays revealed that 50% of the TPA-exposed population was composed of cornified cells as opposed to 8% in untreated controls. A morphologically distinct cell type (TT cell) emerged after TPA treatment which was triangular in shape, did not stratify, appeared to proliferate rapidly and at most TPA concentrations became the predominant cell type within 1-2 wk. Cultures composed predominantly of TT cells formed few cornified envelopes, grew well in the absence of TPA and formed colonies at low cell input. In contrast to its effect on keratinocytes, TPA enhanced TT colony formation three-four fold and decreased the doubling time of TT cells. Studies were performed to determine the origin of TT cells. Immunofluorescent staining indicated that TT cells lacked the keratinocyte antigens keratin, pemphigus and pemphigoid. Tonofilaments and desmosomes were not seen by electron microscopy. The lack of both melanosomes and standard histochemical DOPA oxidase staining indicated that TT cells were probably not of melanocyte origin. Tests used to identify Langerhans cells were negative. Whereas TT cells, as well as dermal fibroblasts, yielded positive immunofluorescence with antibodies to vimentin, TT cells gave a weak histochemical leucine aminopeptidase reaction, while the reaction of fibroblasts exposed to TPA was strong. Treatment of human dermal fibroblasts with TPA did not yield TT cells. The endothelial cell antigen Factor VIII-associated protein was absent by immunofluorescence. These results suggest that the primary effect of TPA on cultured human epidermis is to accelerate terminal differentiation in the keratinocyte population and to stimulate growth of an as yet unidentified cell type. (Author abstract) (25 Refs)

45. TUMOR-PROMOTING PHORBOL ESTERS PROMOTE MELANOGENESIS AND PREVENT EXPRESSION OF THE ADRENERGIC PHENOTYPE IN QUAIL NEURAL CREST CELLS.

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Differentiation; 20(2):117-123 1981

Tumor-promoting phorbol esters were used to manipulate the in vitro development of neural crest cells. When plated at clonal density in secondary culture, quail neural crest cells from the trunk region gave rise to three types of colonies, pigmented, unpigmented, and mixed. Pigmented colonies consisted exclusively of melanocytes; up to 50% of the unpigmented and mixed colonies contained adrenergic nerve cells which could be identified by a catecholamine-specific histofluorescence method. Addition of potent tumor promoters to the culture medium shortened the doubling time of neural crest cells and altered their morphologic appearance. It also delayed the onset of pigmentation, prevented the expression of the adrenerg ic phenotype, reduced the number of unpigmented and mixed colonies, and increased the number of pigmented colonies, most likely by directing progenitor cells preferentially to the melanogenic pathway. There was a clear correlation between the ability of phorbol esters to promote skin tumors in mice and their ability to interfere with the in vitro development of quail neural crest cells. The potent promoters 12-O-tetradecanoyl phorbol 13-acetate (TPA) and phorbol 12,13-didecanoate (PDD) were most effective, phorbol 12,13-diacetate (PDA) was considerably less effective, the nonpromoting analogues 4-O-methyl 12-O-tetradecanoyl phorbol 13-acetate (4-O-Me-TPA) and 4alpha-phorbol 12,13-didecanoate (4alpha-PDD) and the parent alcohol phorbol (PHR) had little or no effect. (Author abstract) (25 Refs)

46. MUTAGENESIS IN FETAL RAT EPIDERMAL CELLS AND EFFECT OF TUMOR PROMOTER, 12-O-TETRADECANOYL-PHORBOL-13-ACETATE (MEETING ABSTRACT).

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Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

The effect of a tumor promoter, 12-0-tetradecanoyl-phorbol-13-acetate (TPA) on the frequency of mutation from 6-thioguanine (6TG) susceptibility to resistance of the aneuploid fetal rat epidermal cells by chemical carcinogens have been examined. Twenty-four hr treatment of wild type cells by 1 ug/ml dimethylbenzanthracene (DMBA) or 0.1 ug/ml N-methyl-N'-nitro-N'-nitrosoguanidine (MNNG) induced 6TG mutants at the frequency of 49.4 x 10(-6) and 21.2 x 10(-6), respectively. The wild type cells totally died in the medium containing more than 0.1 ug/ml 6TG. However, carcinogen-induced 6TGr mutants showed 70% survival in the medium containing 1 ug/ml 6TG. Yield of 6TGr mutants was enhanced under the continuous existence of 10 ng/ml TPA after carcinogen treatment. (no Refs)

47. RELEASE OF HISTAMINE FROM HUMAN LEUKOCYTES STIMULATED WITH THE TUMOR-PROMOTING PHORBOL DIESTERS. II. INTERACTION WITH OTHER STIMULI.

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J Immunol; 128(1):136-140 1982

The tumor promoter and irritant, 12-O-tetradecanoylphorbol-13-acetate (TPA), previously shown to be a potent histamine releaser, has been used to further probe the mechanism of histamine release from human basophils. TPA and the calcium ionophore, A23187, produced a synergistic response in which subeffective concentrations of each stimulus (which alone produced less than 3% release) together produced over 70% histamine release. TPA also synergized with the IgE cross-linking stimulus anti-IgE. Desensitizatio n

of cells by incubation with anti-IgE in the absence of calcium rendered the cells unresponsive to anti-IgE and super-responsive to TPA. This marked increase in the TPA response was the result of an increase in the rate of TPA-induced histamine release, and occurred in the absence of extracellular calcium. The ability of various concentrations of anti-IgE to 'sensitize' cells to TPA paralleled their ability to produce histamine release in untreated cells rather than their ability to desensitize the cells. These results suggest that in the absence of calcium, anti-IgE induces desensitization of some and activation of other elements of the histamine-release process. The anti-IgE dose-response pattern of this activation event further suggests that it is an integral part of the anti-IgE-induced release process itself. (Author abstract) (23 Refs)

48. STUDIES OF HUMAN LEUKEMIC LYMPHOID PROGENITOR CELL DIFFERENTIATION WITH THE PHORBOL ESTER TPA (MEETING ABSTRACT).

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Tenth Annual Meeting, Midwest Autumn Immunology Conference, Oct 18-20, 1981, Minneapolis, Minnesota University of Minnesota; 1981

A major problem plaguing studies of human lymphoid progenitor cells has been the small number of these cells present in normal bone marrow (BM) and the paucity of assays for analyzing their various differentiation pathways. Since the cells involved in non-T, non-B (E-, SIg-) acute lymphoblastic leukemia (ALL) have been hypothesized to represent the malignant counterparts of BM lymphoid progenitor cells, ALL cells may be helpful in studying human lymphopoiesis. We have approached this problem using a panel of cell markers and the phorbol ester 12-O-tetradecanoylphorbol-13-acetate (TPA). Results to be presented clearly show that TPA can induce a number of phenotypic changes in non-T, non-B ALL cells. Such changes may reflect a differentiation-linked expression of cellular structures in normal BM lymphoid progenitor cells. (no Refs)

49. EFFECTS OF 12-O-TETRADECANOYLPHORBOL-13-ACETATE AND MEZEREIN ON GAMMA RADIATION-INDUCED DNA REPAIR IN RESTING BOVINE LYMPHOCYTES.

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Cancer Lett; 15(1):87-93 1982

The effect of the potent tumor promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA) on gamma radiation-induced DNA repair in resting (Go) lymphocytes was studied. Lymphocytes were irradiated with appropriate doses of gamma radiation in order to introduce single-strand breaks in their DNA. The repair of DNA damage was determined by incubating irradiated (500 rad) cultures at 37 C in a water bath and at various times placing them on ice. Mezerein, a non-promoter but a co-mitogen in lymphocy tes was used as a control agent. The cells were lysed immediately following irradiation on linear sucrose gradients and the distance travelled by the nucleotides was determined. The sedimentation ratio was calculated from the distance travelled by nucleoids for irradiated cells to that of unirradiated cells. It was observed that the presence of 1 uM of either TPA or mezerein in lymphocyte cultures following a 1 hr incubation did not produce a significant deviation in sedimentation behavior from dimethyl sulfoxide treated control cultures. Results indicate that neither TPA nor mezerein at 1 uM h have any degenerative effect on the integrity of the cells DNA. The percent recovery of DNA supercoil in nucleoids following 1 hr incubation of irradiated cells was 30-34% whether or not TPA or mezerein was present during recovery period. Results support the hypothesis that the tumor promoting ability of TPA is not a result of impaired repair of potentially mutagenic lesions in DNA. (20 Refs)

50. DECREASED SYNTHESIS OF HIGH-MOLECULAR-WEIGHT GLYCOPEPTIDES IN HUMAN PROMYELOCYTIC LEUKEMIC CELLS (HL-60) DURING PHORBOL ESTER-INDUCED MACROPHAGE DIFFERENTIATION.

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Cancer Res; 42(2):484-489 1982

The human promyelocytic leukemia cell line, HL-60, synthesized a class of high-mol-wt (MW 5,000 to 7,000), N-linked glycopeptides as the major class of protein-bound carbohydrates. Small glycopeptides (MW 2,500 to 3,500), typical of most mammalian cells except RBC, represented a minor component in these cells. The large glycopeptides were labeled efficiently with fucose, glucosamine, and galactose but only poorly with mannose. They were found not to be glycolipids, glycosaminoglycans, or mucin-type glycopeptides and were not susceptible to exoglycosidases, but they were partially degraded by endo-beta-galactosidase. These characteristics are similar to those of the large glycopeptides synthesized by RBC, by another human myeloid leukemia cell line (K562), and by human and murine teratocarcinoma cells. High-mol-wt glycopeptides predominated on another human myeloid leukemia cell line KG1, but they were expressed at low levels on both a human monocytic leukemia cell line (THP-1) and a human T-lymphoblastoid cell line (Jurkat). when HL-60 cells were induced to differentiate into macrophage-like cells with phorbol esters, the proportion of large glycopeptides decreased, and the production of small glycopeptides predominated. This shift was observed within the first several hr after exposure to phorbol esters and was temporally related to the acquisition of adherent properties by the induced cells. In contrast, when HL-60 cells were induced to differentiate into granulocytes by dimethyl sulfoxide, hypoxanthine, or retinoic acid, they continued to synthesize glycopeptides similar to uninduced cells. Human peripheral blood granulocytes synthesized primarily large glycopeptides, whereas monocytes and lymphocytes synthesized mostly small glycopeptides. These results indicate that the synthesis of high-mol-wt glycopeptides is a property of human myeloid leukemia cell lines and that it persists throughout myeloid differentiation. A proportionate decrease in the synthesis of these large glycopeptides is a part of the differentiation program for monocytes and macrophages. (Author abstract) (34 Refs)

51. T-CELL MITOGENS CAUSE EARLY CHANGES IN CYTOPLASMIC FREE CA2+ AND MEMBRANE POTENTIAL IN LYMPHOCYTES.

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Dept. Physiology-Anatomy, Univ. California, Berkeley, CA, 94720
Nature; 295(5844):68-71 1982

Effects of concanavalin A, phytohemagglutinin, mitogenic calcium ionophores (A23187 and ionomycin), and the cocarcinogen 12-O-tetradecanoylphorbol-13-acetate on cytoplasmic Ca++ level and membrane potential in mouse thymocytes

and pig node lymphocytes are reported. Ca++ was measured with the use of a fluorescent indicator (quin2) that was loaded into the cytoplasm of intact cells. (35 Refs)

52. EFFECT OF TUMOR PROMOTER TPA ON COMPLEMENT AND EPSTEIN-BARR VIRUS-RECEPTORS IN HUMAN LYMPHOBLASTOID CELL LINES (MEETING ABSTRACT).

Yamamoto N, Mitsuma T
Institute for Virus Research, Kyoto University, Kyoto, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Effect of tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) on the C3-and Epstein-Barr virus (EBV)-receptors in various human lymphoblastoid cells was investigated using the erythrocyte antibody complement (EAC) rosette formation method and a quantitative bioassay for EBV-receptors. TPA caused a significant decrease of C3-and EBV-receptors in the cultures of both Raji and SB4 cells. Effect of TPA on the reduction of C3-receptors was observed in many other cell lines. In an EBV-negative B cell line, BJAB, significant enhancement of EAC rosette formation was noted, however. The TPA-mediated reduction of C3-receptors in Raji cells was further reduced by various inhibitors of RNA and protein synthesis. (no Refs)

53. MECHANISM OF TUMOR PROMOTION: EFFECT OF 12-O-TETRADECANOYL-PHORBOL-13-ACETATE (TPA) ON IMMUNE RESPONSES IN VITRO (MEETING ABSTRACT).

Yamashita U
Department of Immunology, University O.E.H. Medical School, Kitakyushu, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

In order to further analyze the mechanism of tumor promotion by tumor promoting agents, we studied the effect of TPA on immune responses in vitro in mice. The addition of TPA at the concentration of 1-1000 ng/ml in the in vitro culture suppressed the development of anti-trinitrophenyl (TNP) antibody response which was induced by the secondary stimulation of TNP-KLH-primed spleen cells and the development of TNP-reactive cytotoxic T cell activity which was induced by the culture of responder T cells and TNP-modified stimulator cells. However, the addition of TPA at the same concentration did not suppress the antigen specific and mitogen-induced proliferative T cell responses, but enhanced them. Other compounds; Phorbol, Phorbol-12-myristate, Phorbol-13-acetate, were neither immunosuppressive nor stimulative on lymphocytes. These results suggest that the tumor promoting agents regulate tumor promotion by two mechanisms: one is the suppression of the immune surveillance mechanism of the host and the other is the stimulation of the transformed cells. (no Refs)

54. THE RELATIONSHIP BETWEEN TUMOR PROMOTER BINDING AND EPSTEIN-BARR VIRUS INDUCTION IN HUMAN LYMPHOBLASTOID CELL LINES.

Yamamoto N, Bauer G
Institut fur Virologie, Zentrum fur Hygiene der Universitat Freiburg, Hermann-Herder-Str. 11, 7800 Freiburg, W. Germany
J Cell Physiol; 109(3):397-402 1981

Epstein-Barr virus (EBV) nonproducer Raji, and its derivative NC-37 cells, were incubated with 3H-TPA (12-O-tetradecanoyl-phorbol-13-acetate), and cell associated radioactivity determined. TPA dissociation was studied by centrifuging previously incubated cells, and resuspending them in fresh medium to the original concentration. Free and bound 3H-TPA were measured radiometrically. Serum components alone can bind TPA within 60 min, but cells can complete for part of this TPA. Binding of TPA to cells is temperature dependent; absence of serum approx doubles the rate of TPA binding. Dissociation of TPA from cells is rapid, and is greater in the presence of serum. (24 Refs)

55. SPECIFIC BINDING OF THE TUMOR PROMOTER TPA IN VARIOUS MOUSE ORGANS AS MEASURED BY A 'COLD ACETONE-FILTER ASSAY'.

Hergenhahn M, Hecker E
Inst. Biochemistry, German Cancer Res. Center, D-6900 Heidelberg, W. Germany
Carcinogenesis; 2(12):1277-1281 1981

Rapid, specific, saturable and partially reversible binding of the tumor promoter 12-O-tetradecanoylphorbol-13-acetate ([3H]TPA) to a particulate fraction of mouse brain can be demonstrated by means of a 'cold acetone-filter assay'; by washing with cold acetone at-20 C, nonspecific binding of the highly lipophilic [3H]TPA to membranes can be reduced to approx 10% of the total binding. A comparative study of homogenates of several organs with this test revealed specific [3H]TPA binding/ug DNA in the order; brain is much greater than lung, which is approx = spleen, which is approx = liver, wh ich is approx = kidney, which is approx = thymus, which is approx = ovaries. Specific binding sites were also detected in 600 x g supernatant fractions of homogenates from epidermis, forestomach, glandular stomach and small intestine. Competition experiments showed displacement of [3H]TPA by TPA greater than phorbol-12,13-didecanoate greater than 12-deoxyphorbol-13-tetradecanoate greater than phorbol-12,13-dibutyrate (PDBu) greater than phorbol-12,13-diacetate greater than 4-O-methyl-TPA greater than 4alpha-phorbol-12,13-didecanoate in the brain particulate fraction. Specific [3H]TPA binding is sensitive to heat, periodate and dithiothreitol, but is relatively insensitive to urea or to 1-5% soln of several common detergents. It is estimated that the present binding test is approx 500x more sensitive than the widely-accepted [3H]PDBu assay; perhaps more important, the present method employs TPA, which is extremely effective both as a tumor promoter in vivo and as a pleiotropic effector of cells in vivo and in vitro. (Author abstract) (18 Refs)

56. TISSUE AND SPECIES DISTRIBUTION AND DEVELOPMENTAL VARIATION OF SPECIFIC RECEPTORS FOR BIOLOGICALLY ACTIVE PHORBOL AND INGENOL ESTERS.

Shoyab M, Warren TC, Todaro GJ
Lab. Viral Carcinogenesis, NCI, Frederick, MD, 21701
Carcinogenesis; 2(12):1273-1276 1981

A new and rapid binding assay for [3H]phorbol-12,13-dibutyrate (PDBu) binding to its receptors in cell or tissue homogenates or subcellular fractions is described. PDBu binding sites are widely distributed in mouse tissues. Brain and spleen contain exceptionally high concentrations of these receptors. PDBu receptors are present in all regions of the brain. The choroid plexus and pituitary bind markedly lower amounts of PDBu than other brain regions. Brains or spleens from different murine strains bind almost the same amounts of PDBu while those organs from embryonic mice bind very little

PDBu. Binding increases with age and reaches a maximum at approx 4 wk of age. Young and mature brains from various species contain these specific binding sites. These data suggest a structural or enzymatic role for PDBu receptors. (Author abstract) (18 Refs)

57. INHIBITION OF ELECTRICAL CELL COUPLING BY TUMOR PROMOTING-AGENTS (MEETING ABSTRACT).

Kanno Y, Enomoto T, Yamasaki H
Department of Physiology, Hiroshima University School of Dentistry, Hiroshima, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

The effect of tumor promoting agents on electrical coupling between human FL cells was investigated. The cells dissociated with 0.02% EDTA were contacted by gentle centrifugation and the pair cells contacted were cultured in Eagle's minimum essential medium supplemented with 10% calf serum. I n control medium, most pair cells established electrical coupling by 3 hr after culture. 12-0-tetradecanoyl phorbol-13-acetate (TPA) inhibited the formation of cell coupling without changing membrane potential and membrane resistance. Cell coupling recovered to control level 4 hr after the removal of TPA. When cells that already established cell coupling were treated with TPA, cell coupling was suppressed. Inhibition of electrical coupling was observed with other related promoters. It appears that TPA and other related tumor promoters specifically suppress electrical coupling without affecting electrical properties of cell membrane. (no Refs)

58. PREVENTION OF TUMOR PROMOTER-MEDIATED INHIBITION OF PREADIPOCYTE DIFFERENTIATION BY DEXAMETHASONE.

Hiragun A, Sato M, Mitsui H
Dept. Cell Biology, Tokyo Metropolitan Inst. Medical Science, Honkomagome 3-18-22, Bunkyo-ku, Tokyo 113, Japan
Gan; 72(6):891-897 1981

A clonal cell line of murine fibroblast (ST 13) undergoes a terminal differentiation into adipose cells in culture. A tumor promoter, 12-O-tetradecanoyl phorbol 13-acetate (TPA), reversibly inhibited the differentiation of ST 13 preadipocytes. The inhibition of differentiation was accompanied by changes in cell morphology and growth properties and by suppression of cellular insulin binding activity. Dexamethasone (DXM) could prevent the inhibition by TPA of preadipocyte differentiation, concomitant with prevention of the morphological changes and an increase in insulin binding activity. TPA-induced plasminogen activator (PA) secretion and DXM-mediated inhibition of PA activity could not be correlated with inhibition/prevention-of-inhibition of differentiation. (Author abstract) (31 Refs)

59. TUMOR PROMOTERS INCREASE THE SYNTHESIS OF A PROTEIN OF 32,000 DALTONS IN MOUSE FIBROBLASTS (MEETING ABSTRACT).

Hiwasa T, Sakiyama S, Fujimura S
Division of Biochemistry, Chiba Cancer Center Research Institute, Chiba, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

In order to investigate the effect of tumor promoter phorbol esters on gene expression, newly synthesized polypeptides of Balb/c 3T3 A31 cells labeled with [35S]methionine after the addition of tumor promoters were analyzed by one- or two-dimensional polyacrylamide gel electrophoresis. The increased synthesis of a protein (32K protein) whose mol wt is 32,000 daltons was noted as an earliest change among various responses to tumor promoters. The synthesis of 32K protein increased approx 3-fold by the treatment with 20 ng/ml of tetradecanoylphorbol acetate for 2 hr. This increase was inhibited by actinomycin D and tumor promoter-treated cells contained higher level of translatable messenger RNA coding for 32K protein than control cells, suggesting that the elevated synthesis of 32K protein caused by tumor promoters is regulated at the transcriptional level. (no Refs)

60. EFFECTS OF RETINOIC ACID AND TUMOR PROMOTER 12-O-TETRADECANOYLPHORBOL-13-ACETATE (TPA) ON THE CELL CYCLE OF HELA CELLS.

Kinzel V, Krombholz-Nolinski I, Stohr M, Richards J
German Cancer Res. Center, Inst. Experimental Pathology, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany
Int J Cancer; 29(1):93-99 1982

The influence of retinoic acid (RA), a modifier of tumor promotion, on the cell cycle of HeLa cells, and its ability to interfere with the early irradiation-like effects induced by the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) has been investigated by a variety of different techniques. These include measurement of thymidine incorporation and uptake, of labeling and mitotic indices, and of DNA histograms by flow cytometry. Within 24 hr RA (2 x 10(-5) M) alone caused a short-lasting inhibition of DNA synthesis; later a decrease of cells in S phase and a steady descending mitotic activity were observed. On combined treatment with RA and TPA (10(-8) M), the latter seems to dominate RA in two instances: (1) the transient G2 blockage due to TPA is seen as the earliest effect; however, the cultures do not seem to recover as well if RA is also present; (2) the TPA-induced GI blockage appears to be effective but less pronounced in the presence of both chemicals. Where the third typical TPA-induced effect is concerned, however, both compounds seem to act to a comparable degree in the same time frame; namely by an initial inhibition of DNA synthesis which thus might be a point of critical interference if promoter and modifier are given together. (Author abstract) (44 Refs)

61. TESTING FOR TUMOR PROMOTERS IN EUPHORBIA LATHYRIS: ANALYSIS OF POSSIBLE HEALTH HAZARDS.

Bissell MJ, Nemethy EK, Riddle L, Calvin M
Lab. Cell Biology, Div. Biology and Medicine, Univ. California, Berkeley, CA, 94720
Bull Environ Contam Toxicol; 27(6):894-902 1981

The use of a system for detection of promoter activity in Euphorbia lathyris extracts before and after treatment with organic solvents in the preparation of synthetic fuels is described. The system is based on the known effects of 12-O-tetradecanoyl-phorbol-13-acetate (TPA), the most active component of croton oil. Basic hydrolysis of the crude active fraction (ELA) of dry latex from E lathyris yielded one compound identified as ingenol triacetate by spectroscopic methods. The morphological effects of ELA on chick embryo fibroblasts were compared with the effects of TPA on the same cells. ELA appears to be active. Comparison of the rates of sugar uptake after treatment with ELA indicated that ELA possesses tumor promoter activity and the activity is lost after drying and extraction. Response to ELA was also teste d on temperature sensitive mutants of Rous sarcoma virus. Results indicate that after

mechanical harvesting and drying no toxicological dangers should exist. (16 Refs)

EPIDEMIOLOGIC DATA CONCERNING MODIFICATION OF CARCINOGENESIS

62. DIET AND CANCER OF THE LARGE BOWEL.

Zaridze DG
Analytical Epidemiology Programme, Div. Epidemiology and Biostatistics, International Agency for Res. on Cancer, 150 Cours Albert Thomas, 69372 Lyon, Cedex 2, France
Nutr Cancer; 2(4):241-249 1981

Suspected etiological and protective factors in large bowel cancer are reviewed. Incidence of large bowel cancer correlates with consumption of fat, protein or meat. Etiological hypotheses propose that high-fat diet is related to an increased risk of large bowel cancer, while analysis of the geographical distribution of colon cancer in humans. The results of further epidemiological studies do not unequivocally support the hypotheses. Control studies do not confirm an association between diet and the colorectal cancer risk at the individual level. Lack of uniformity among the findings of epidemiological studies concerned with the role of diet could be explained by lack of sensitive and reproducible methods for assessment of diet in epidemiological studies and lack of knowledge of the mode of action of dietary factors responsible either for the development of the tumor or for protection against it. Research on large bowel cancer in humans is focused on the promoting factors. Initiators could be the factors responsible for the individual risk for colon cancer in populations with homogeneous high-fat diet practices. Available data indicate adenomatous polyps and non-invasive carcinoma of the large bowel could remain stationary. Future epidemiological research on diet and large bowel cancer should deal with more precisely defined hypotheses in which the multifactorial nature of the tumor would be taken into account. (49 Refs)

63. CARCINOMA OF THE COLON AND RECTUM (MEETING ABSTRACT).

Fisher E
No affiliation given
Current Concepts in Cancer Therapy, December 10-12, 1981, St Louis, Missouri Washington University School of Medicine; 1981

Colorectal carcinoma attributes to 14% of all deaths due to cancer in the United States. The peak incidence of this disease is in the seventh decade with 8% diagnosed before age forty. Certain disease definitely predispose to development of colorectal carcinoma; familial polyposis, Gardner's syndrome and vilous adenomas. In some cases, adenomatous polyps may be premalignant lesions. Colorectal carcinoma is more common in urbanized civilizations than in rural areas. It is felt that diets low in roughage and high in sugar may be carcinogenic by prolonging contact of fecal material with colonic mucosa and promoting action of neoplastic agents. Possible carcinogens could be formed from bile by bacterial g rowth or derived from foods. Seventy per cent of colorectal cancers are found in the distal colon and rectum. The most common site of metastasis is to regional lymph nodes. Lymph nodes are involved in over 90% of cases where carcinoma has spread through the bowel wall. In cases where the lesion is confined to the bowel wall, positive nodes are present in over 45% of the cases. Positive nodes are often found some distance from the primary site with intervening normal nodes. For this reason, long segments of colon are removed. The size of the primary tumor does not correlate well with either incidence of metastases or survival. Prognosis is fairly well predicted by the Dukes Classification and it can be used at the operating table as a guide to the proper operation. Final classification of the tumor is done after permanent histologic slides are examined. (no Refs)

REVIEWS AND OTHER RELATED STUDIES

64. THE NATURAL HISTORY OF CARCINOGENESIS: IMPLICATIONS OF EXPERIMENTAL CARCINOGENESIS IN THE GENESIS OF HUMAN CANCER.

Pitot HC, Goldsworthy T, Moran S
McArdle Lab. for Cancer Res., Dept. Oncology, Medical Sch., Univ. Wisconsin, Madison, WI, 53706
J Supramol Struct Cell Biochem; 17(2):133-146 1981

Implications of the natural history of carcinogenesis with respect to human cancer are reviewed. Topics include stages in the natural history of carcinogenesis (definitions: initiation, promotion, progression), implications of stages in the natural history of carcinogenesis, characteristics of the stages and of initiation and the initiated cell, the role of cell division in initiation of neoplasis, characteristics of tumor promotion and promoting agents, dose response to promoting agents, reversibility of the promotion stage, models for the study of the molecular mechansims of tumor promotion, and implications of the characteristics of the stages of carcinogenesis. Model systems exhibiting a two-stage mechanism of carcinogenesis are described and promoting agents known to occur in the human environment are listed. (77 Refs)

65. A NEW PROTOCOL AND ITS RATIONALE FOR THE STUDY OF INITIATION AND PROMOTION OF CARCINOGENESIS IN RAT LIVER.

Potter VR
McArdle Lab. Cancer Res., Univ. Wisconsin Medical Sch., Madison, WI, 53706
Carcinogenesis; 2(12):1375-1379 1981

A new protocol for carcinogenesis in rat liver is described in order that confirmatory experiments might be undertaken concurrently. The basic protocol, designated IPI (initiator plus promoter plus initiator), is presented in several alternative forms including the possible use of x-irradiation as the initiator. The rationale is discussed in terms of the two-hit somatic mutation theory of Armitage and Doll, with an initial hit produced by the first dose of initiator and expansion of single cells to sizable clones by promotion thereby increasing the probability of a second hit by the second dose of initiator. The question of relevant mutations is taken up and it is proposed that genes for chalones and for chalone receptors are logical targets for consideration in a two-mutation sequence. (Author abstract) (33 Refs)

66. CURRENT CONCEPTS AND CONTROVERSIES IN CHEMICAL CARCINOGENESIS.

Weinstein IB
Div. Environmental Sciences, Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032
J Supramol Struct Cell Biochem; 17(2):99-120 1981

Fundamental research at the cellular and molecular levels on mechanisms of action of chemical carcinogenesis and applied aspects and the concept of 'molecular epidemiology' of cancer are reviewed. The action of initiating agents and their metabolism and covalent binding to macromolecules is discussed under the following headings: metabolic activation, carcinogen potency, structures of carcinogen-DNA adducts, conformational changes in DNA, carcinogen modification of mitochondrial DNA, DNA repair, and carcinogen-DNA modification and mechanism of initiation. Tumor promotion and multifactor interactions are discussed in relation to two-stage skin carcinogenesis. Numerous effects elicited by phorbol ester tumor promotors, particularly 12-O-tetradecanoyl-phorbol-13-acetate, are classified into three categories: mimicry of transformation, modulation of differentiation, and membrane effects. Also considered in relation to phorbol ester tumor promotors, tumor promotion, and multifactor interactions are phorboid receptors, ion flux, possible role of kinases, chromosomal effects and activated oxygen, and chemical-viral interactions. The tumor-promoting activity of polycyclic aromatic hydrocarbons is discussed. A unified theory of tumor initiation and promotion is presented. Molecular epidemiology and cancer prevention are discussed with regard to limitations of current approaches and molecular cancer epidemiology. (94 Refs)

67. CELLULAR TRANSFORMATION BY RADIATION: INDUCTION, PROMOTION, AND INHIBITION.

Borek C
Radiological Res. Lab., Cancer Center/Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032
J Supramol Struct Cell Biochem; 16(4):311-336 1981

Steps and factors in radiation transformation are reviewed. Recent and current studies using mammalian cell cultures are described: subjects include oncogenic transformation (TR) of animal cells in vitro, quantitative studies in radiation TR, modification of TR by the protease inhibitor antipain, nutritional factors such as retinoids, and thyroid hormone as a modulator of carcinogenesis. Oncogenic TR of human cells in vitro is discussed. (61 Refs)

68. ARACHIDONIC ACID TRANSFORMATION AND TUMOR PRODUCTION.

Levine L
Dept. Biochemistry, Brandeis Univ., Waltham, MA, 02254
Adv Cancer Res; 35:49-79 1981

The relationship between arachidonic acid (AA) and cancer is reviewed. Biochemical pathways of AA leading to endoperoxides and several substrates of the lipoxygenases are presented, and prostaglandin (PG) levels in tumors are discussed. AA transformation in relation to hypercalcemia and tumor production is reviewed. Discussion includes the effects of 12-O-tetradecanoyl phorbol-13-acetate (TPA) on PG production of cells in vitro and in vivo and the effect of inhibitors of PG production on TPA activity in cultured cells. Stimulation of PG production by growth factors, the effects of PG on cell or tumor growth, and the relationship between PG and immune response are reviewed. Acylhydrolase activity, or possibly cylooxygenase activity, is more likely than lipoxygenase activity to be causally related to cancer. Future studies concentrating on the mechanism of inhibition of acylhydrolase activity may be important for control of tumor growth. (209 Refs)

69. HORMONAL GENESIS OF BREAST CANCER (MEETING ABSTRACT).

Mauvais-Jarvis P
Department of Reproductive Endocrinology, Hopital Necker, 75015 Paris, France
Third Meeting of the French Society of Senology and Mammary Pathology, October 15-17, 1981, Versailles, France Centre Rene Huguenin; 1981

This paper relates the different lectures given in December 9, 1980 by the speakers invited by the Breast Cancer Task Force Committee (Bethesda, MD) to participate in a workshop on luteal phase defects and breast cancer risks. The role of unopposed estrogen effect as a major promoting factor in human breast carcinogenesis is emphasized - particularly in terms of duration of exposure, especially during the first 'estrogen window' which precedes the first full term pregnancy. In the same conception, benign breast disease seems to be provoked by a progesterone insufficiency due either to the 'physiological' estrogen window occurring either after the beginning of breast development and during the perimenopausal period, or after stress exposure of women at any time of their reproductive life. In terms of prevention, the therapeutical use of progesterone and synthetic progestins in women presenting either a benign breast disease or a high risk of breast cancer is proposed in particular during the perimenarcheal period of the reproductive life. (no Refs)

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As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. ETHYLENE OXIDE (ETO): EVIDENCE OF CARCINOGENICITY.
Coene RF
National Inst. for Occupational Safety and Health, Cincinnati, OH
Vet Hum Toxicol; 23(6):439-443 1981

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American Health Foundation, Naylor Dana Inst Disease Prevention, Valhalla, NY, 10595
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6. MALIGNANT MELANOMA.
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Compr Ther; 7(12):36-44 1981

7. MELANOTIC TUMORS OF THE UVEA AND RETINA.
Schmitt H
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CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

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In FIN

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MODIFICATION OF CARCINOGENESIS

SERIES CK04 No. 82/07

JULY, 1982

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MODIFICATION OF CARCINOGENESIS BY CHEMICAL AGENTS OR IRRADIATION

1. METHAPYRILENE EFFECTS ON INITIATION AND PROMOTION OF GAMMA-GLUTAMYL-TRANSPEPTIDASE POSITIVE FOCI IN RAT LIVER.

Couri D, Wilt SR, Milks MM
Div. Toxicology, Dept. Pharmacology, Coll. Medicine, Ohio State Univ., Columbus, OH, 43210
Res Commun Chem Pathol Pharmacol; 35(1):51-61 1982

The initiating and promoting effects of methapyrilene were evaluated using the hepatic enzyme-altered foci bioassay. Male Sprague-Dawley rats were partially hepatectomized and 24 hr later were administered either methapyrilene or nitrosodiethylamine by oral gavage. Subsequently, the animals were promoted with 500 ppm phenobarbital or 200 ppm methapyrilene in drinking water for 8 wk. Fresh frozen sections of liver were then stained and scored for gamma-glutamyl-transpeptidase (GGT)-positive foci. Methapyrilene, when tested as the nominal initiator at a single dose of 50 mg/kg or at two doses of 130 mg/kg and promoted by phenobarbital, did not induce foci above background levels. However, when substituted for phenobarbital as the promoting agent following nitrosodiethylamine initiation, methapyrilene enhanced enzyme-altered foci formation to an equal or greater extent than did the promoter phenobarbital. These results suggest that the carcinogenic effects of methapyrilene may be related to its ability to enhance hepatic tumorigenesis. (Author abstract) (19 Refs)

2. PROMOTION BY POLYCHLORINATED BIPHENYLS OF ENZYME-ALTERED FOCI IN RAT LIVER.

Pereira MA, Herren SL, Britt AL, Khoury MM
Health Effects Res. Lab., U.S. Environmental Protection Agency, 26 West St. Clair St., Cincinnati, OH, 45267
Cancer Lett; 15(2):185-190 1982

The number of gamma-glutamyltranspeptidase (GGTase)-positive foci was examined in livers of partially hepatectomized male Sprague-Dawley rats given an initiating dose of diethylnitrosamine (DENA: 0.3 millimole/kg body wt, po) followed 7, 28, or 49 days later by one to three doses of Aroclor 1254 (500 mg/kg, ip). Rats were killed 21 days after the last dose of Aroclor. Incidence of GGTase-positive foci increased from a mean of 0.70 foci/square cm (cm2) liver in solvent (tricaprylin)-treated, partially-hepatectomized, DENA-initiated controls to 2.28 foci/cm2 in animals given a single dose of Aroclor 1254. Maximum enhancement was obtained after two doses, which resulted in 3.47 foci/cm2. Up to three doses of Aroclor did not increase the incidence of GGTase-positive foci in partially-hepatectomized animals that had not received DENA. Aroclor 1254 appears suitable as an inexpensive promotor in a short-term initiation/promotion assay for chemical carcinogens. (20 Refs)

3. STRAIN AND SPECIES DIFFERENCES IN THE INDUCTION OF ATPASE-DEFICIENT HEPATIC FOCI BY DIETHYLNITROSAMINE.

Laib RJ, Brockes B, Schwaier A, Bolt HM
Abteilung fur Toxikologie, Pharmakologisches Institut, Universitat Mainz, Obere Zahlbacher Strasse 67, D-6500 Mainz 1, W. Germany
Cancer Lett; 15(2):145-148 1982

Quantitation of nucleoside-5'-triphosphate (ATPase)-deficient foci for determination of hepatocarcinogenicity in species other than the rat was examined. Rats, mice, guinea pigs, and tupaias received 5 mg/kg diethylnitrosamine ip 5 days/wk for 3 wk and were killed 6 and 12 wk after treatment was stopped. No ATPase-deficient hepatocellular foci occurred in either of the mouse strains tes ted (NMRI and B6C3F1) or in tupias. A few foci were observed in guinea pigs 12 wk after cessation of carcinogen treatment. Both rat strains tested developed significantly greater numbers of foci 6 and 12 after carcinogen administration than control rats. Sprague-Dawley rats developed more foci than Wistar rats, and female rats of both strains showed a greater response than males. Quantitation of ATPase-deficient hepatocellular foci as a determinant of hepatocarcinogenesis is restricted to the rat species. (10 Refs)

4. REGULATION OF RAT ALPHA-FETOPROTEIN PRODUCTION BY METHIONINE DURING ETHIONINE-HEPATOCARCINOGENESIS.

Miyazaki M, Watanabe A
Div. Pathology, Cancer Inst., Okayama Univ., Okayama 700, Japan
Int J Cancer; 29(2):213-216 1982

The levels of serum alpha-fetoprotein (AFP) in rats were determined during hepatocarcinogenesis with ethionine, and the effects of methionine administration on serum AFP elevation in these animals were studied with the aim of investigating regulatory mechanisms of AFP production during carcinogenesis. Elevation of serum AFP was observed 6 wk following the start of feeding a diet containing 0.25% ethionine and again at the 22nd wk of feeding, when a well-differentiated hepatoma had already developed. These biphasic elevations of serum AFP concentrations in rats fed a 0.25% ethionine-containing diet decreased abruptly and significantly following a change to the basal diet either supplemented with or without 0.7% methionine. The possibility that regulation of AFP production in these rats may correlate with methionine metabolism is discussed on the basis of the experimental data obtained. (Author abstract) (17 Refs)

5. ACUTE EFFECTS OF SELECTED HEPATOTOXIC AGENTS ON POLYRIBOSOMES AND PROTEIN SYNTHESIS IN THE LIVERS OF RATS FED PURIFIED DIETS CONTAINING HEPATOCARCINOGENS.

Sidransky H, Verney E
Dept. Pathology, George Washington Univ. Medical Center, Washington, DC, 20037
Exp Mol Pathol; 36(1):72-85 1982

This investigation was concerned with the effects of certain hepatocarcinogens ingested for long- or short-term intervals upon selected responses of rat liver to specific hepatotoxic stimuli. Rats fed ad libitum for long (3 to 45 wk) periods or force-fed for short (3 days) periods purified diets containing a single hepatocarcinogen, ethionine, N-2-fluorenylacetamide, 3'-methyl-4-dimethylaminoazobenzene, or thioacetamide, were subjected to the acute administration of a single hepatotoxic agent, such as puromycin, actinomycin D, sparsomycin, hypertonic NaCl or CCl4, and hepatic protein synthesis (in vitro) and polyribosomal aggregation were evaluated. Relating to in vitro protein synthesis, in long-term experiments, puromycin induced less inhibition in the experimental groups than in the control (basal diet) group; and actinomycin D inhibited all groups similarly; while in the short-term experiment s, puromycin induced less inhibition in the experimental groups than in the control group; actinomycin D inhibited the basal and ethionine groups more than the other groups; sparsomycin induced variable degrees of inhibition, with the ethionine group showing the most and the N-2-fluorenylacetamide and thioace-

tamide groups showing the least; hypertonic NaCl markedly inhibited all groups similarly; and CCl4 induced somewhat variable degrees of inhibition, with the thioacetamide group showing less than the other groups. In a few long-term experiments where hepatomas were evaluated in relation to surrounding liver tissue, puromycin administration induced less inhibition in the hepatomas than in the surrounding liver while actinomycin D administration induced similar inhibition in both groups. In general, in all experiments the degree of polyribosomal disaggregation was parallel to that of inhibition of protein synthesis (in vitro). The results reveal that the livers of rats fed purified diets containing selected hepatocarcinogens responsed in a variable manner in regard to protein synthesis (in vitro) and status of polyribosomal aggregation to the acute administration of selected hepatotoxic agents. (Author abstract) (23 Refs)

6. CORRELATION BETWEEN RETINOID INHIBITION OF N-METHYL-N-NITROSOUREA-INDUCED MAMMARY CARCINOGENESIS AND LEVELS OF RETINOIC ACID BINDING PROTEINS.

Mehta RG, McCormick DL, Cerny WL, Moon RC
Lab. Pathophysiology, Life Science Div., IIT Res. Inst., 10 West 35th St., Chicago, IL, 60616
Carcinogenesis; 3(1):89-91 1982

A correlation was made between the ability of retinoids to suppress N-methyl-N-nitrosourea (MNU)-induced mammary carcinogenesis and the levels of cytosolic retinoic acid binding proteins (cRABP) in the cytosol of MNU-induced mammary tumors. Although retinyl acetate and N-(4-hydroxyphenyl)retinamide were found to be effective inhibitors of mammary carcinogenesis in intact hosts, both retinoids were significantly more active in ovariectomized rats than in intact animals. Quantitative analyses of cRABP in the tumors indicated that mammary cancers arising in animals which were ovariectomized 1 wk after MNU administration contained significantly increased concentrations of cRABP compared to cancers appearing in intact rats. In addition, when animals bearing palpable mammary tumors were ovariectomized, the tumors which continued to grow contained significantly higher levels of cRABP than did tumors which stopped growing or regressed. These data suggest that the selective inhibition of ovarian hormone-independent mammary cancer by retinyl acetate and N-(4-hydroxyphenyl)retinamide may be mediated through an increased level of cRABP in tumor cells of ovariectomized hosts. (Author abstract) (21 Refs)

7. INHIBITORY EFFECTS OF SOME NEW RETINOIDS ON CARCINOGENESIS.

Cai H, Zhang J, Cui X
Chemical Etiology Lab., Cancer Res. Inst., Chinese Acad. Medical Sciences, Beijing, People's Republic of China
Yaoxue Xuebao; 16(9):648-653 1981

Retinoic acid has been shown to have an inhibitory effect on the chemically induced cancerous transformation of the squamous epithelium of the murine forestomach. However, due to its toxic side effects, this agent cannot be used clinically. Derivatives of retinoic acid that are less toxic but still possess activity against neoplastic transformation of the murine forestomach are described. Female Swiss mice were used. Of nine retinoic acid derivatives tested, five exhibited significant inhibitory effects on neoplastic transformation, with N-(4-ethoxycarbophenyl) retinamide (RI) particularly active. The effects of RI were reproducible and no toxicity was observed at the therapeutic dosage (1.1 x 10(-4) M/kg); even high doses (up to 6x the therapeutic dose) did not produce hypervitaminosis A, whereas retinoic acid at comparable doses produced marked hypervitaminosis A. One of the active derivatives caused marked inhibition of DNA synthesis in epithelial cells of the murine forestomach, as shown by autoradiography using tritium-labeled thymidine. (13 Refs) (In CHI)

8. STUDY ON ANTIBLASTOMOGENIC ACTION OF EPIDERMAL CHALONES. II. EFFECT OF EPIDERMAL CHALONES ON CARCINOGENESIS IN THE VAGINA.

Okulov VB, Anisimov VN, Chepik OF
Lab. Experimental Tumours, Petrov Res. Inst. Oncology, 68, Leningradskaya St., Pesochny-2, Leningrad 188646, USSR
Exp Pathol; 20(1):1-5 1981

The effect of epidermal or liver G1 and G2 chalone-containing extracts (CCE), prepared from rat skin and liver, upon dimethylbenzanthracene (DMBA)-induced carcinogenesis in the vagina of BALB/c mice was studied. One percent solutions of CCE in PBS were administered intravaginally on polyurethane sponges twice a week during the course of intravaginal applications of DMBA or after its completion up to the death of mice. When administered during the course of DMBA treatment, skin CCE prolonged the latency of cervicovaginal tumors in comparison with liver CCE (48.0 +-0.37 and 44.8 +-0.54 days, respectively (p less than 0.05)). When administered after the course of DMBA application, skin CCE prolonged the lifespan of mice bearing cervicovaginal squamous cell carcinomas in comparison with liver CCE (192 +-12.3 and 161 +-9.0 days, respectively (p less than 0.05)). Skin CCE did not possess any general toxic effect on mice, and they were bearing CCE applications for rather a long period without visible side effects. (Author abstract) (21 Refs)

9. MUTAGENIC EFFECTS OF COMBINATIONS OF CHEMICAL CARCINOGENS AND ENVIRONMENTAL POLLUTANTS IN MICE AS SHOWN BY THE MICRONUCLEUS TEST.

Watanabe M, Honda S, Hayashi M, Matsuda T
Dept. Community Medicine, Toyama Medical and Pharmaceutical Univ., Toyama, Japan
Mutat Res; 97(1):43-48 1982

Combinations of dimethylnitrosoamine (DMN) or N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and CdCl2 or polychlorinated biphenyls (PCB) were force-fed to male ddY mice. The Schmidt method of determining polychromatic erythrocytes (PCEs) in bone marrow cells was used to measure mutagenicity. DMN alone gave a clear dose-dependent response, whereas Cd alone did not; Cd + DMN enhanced the PCE frequency over that for the equivalent concentration of DMN alone. Possible enhancement of MNNG effects by Cd was also observed. PCB alone had almost no effect, and no synergistic or additive effect with DMN or MNNG was seen. Corn oil seemed to inhibit DMN activity. The results suggest that some combinations of carcinogens and environmental pollutants can interact in mutagenic activity. (4 Refs)

MODIFICATION OF CARCINOGENESIS BY DIETARY COMPONENTS OR DIGESTIVE FACTORS

10. BILE SALTS AND OTHER CONSTITUENTS OF THE COLON AS TUMOR PROMOTERS.

Reddy BS, Tanenbaum SR, Montesano R, Correa P, Haenszel W, Wattenberg LW
Div. Nutrition, American Health Foundation, Naylor Dana Inst. for Disease Prevention, Valhalla, NY, 10595
Banbury Rep; 7:345-363 1981

The mechanisms by which dietary components increase the risk of developing colon cancer are reviewed and etiologic factors in large-bowel carcinogenesis are discussed. Dietary fat and fiber affect fecal bile acid excretion, which may then affect carcinogenesis. Cholesterol and its metabolites are mutagenic and have colon-tumor-promoting activity. Fecal mutagens and comutagens in high- and low-risk populations for colon cancer were studied. (63 Refs)

11. FAT, FIBER, AND OTHER MODIFIERS OF INTESTINAL CARCINOGENESIS: A STRATEGY FOR PREVENTION.

Nigro ND, Van Soest PJ, Kingston DG, Bruce WR, Tannenbaum SR, Hill MJ
Dept. Surgery, Sch. Medicine, Wayne State Univ., Detroit, MI, 48201
Banbury Rep; 7:83-93 1981

Published reports on the effects of diet on intestinal carcinogenesis in rats (a process requiring a carcinogen) suggest that the influence of dietary fiber is much smaller than the influence of dietary fat. A high-fiber diet shows a protective effect only when the dietary fat level is low. The effect of a high-fat diet may be mediated through the presence of large amounts of steroids in the large intestine, interacting with the bacterial flora. Epidemiologic data on colorectal cancer in populations having different dietary habits tend to support the results of animal experiments. Further studies are needed to define the relative proportions of dietary fat and fiber for the optimal prevention of colorectal cancer. If only the levels of dietary fat and fiber are changed, it is clear that the changes must be substantial; one report suggests that a 50% reduction in fat and the consumption of bran would be required to reduce t he incidence of colorectal cancer in a high-incidence population. Such drastic changes are unlikely to be accepted by the general population or even persons at high risk. It is suggested that a diet containing bran, a less stringently reduced amount of fat, and vegetables inducing benzopyrene hydroxylase in the large intestine (including cabbage, cauliflower, broccoli, and brussels sprouts) may be more acceptable, at least by persons at high risk of colorectal cancer. (28 Refs)

12. INHIBITORS OF GASTROINTESTINAL NEOPLASIA.

Wattenberg LW, Lipkin M, Goldin BR, Tannenbaum SR, Magee PN, Balish E
Dept. Lab. Medicine and Pathology, Univ. Minnesota Medical Sch., Minneapolis, MN, 55455
Banbury Rep; 7:153-165 1981

Chemical carcinogenesis in the mouse forestomach is inhibited by a wide variety of agents, including phenols, lactones, disulfiram (DSM) and derivatives, aromatic isothiocyanates, indoles, and sodium cyanate. Intestinal carcinogenesis in rats and mice is inhibited by DSM and related compounds, butylated hydroxyanisole, butylated hydroxytoluene, vitamin E, and selenium salts. Many plant materials consumed by humans contain quercetin, which induces intestinal and bladder tumors in rats and may be the carcinogenic component of bracken fern. The addition of phenothiazine to the diet can inhibit the action of quercetin in mice. The role of intestinal microflora in the production or activation of chemical carcinogens requires further investigation. If the microflora are shown to be involved in intestinal carcinogenesis in humans, antibiotics acting on the intestinal microflora might have a protective effect against intestinal carcinogenesis. Many inhibitors of carcinogenesis have been discovered, often on the basis of empirical work. Some of these inhibitors have the advantage of very low toxicity. (36 Refs)

13. DISCUSSION: COLONIC ACTIVATION OF CARCINOGENS.

Wogan GN, Montesano R, Goldin BR, Reddy BS, Magee PN, Archer MC, Goldman P, Balish E, Newmark H, Venitt S, Wattenberg LW, Strobel HW
Massachusetts Inst. Technology, Boston, MA
Banbury Rep; 7:167-172 1981

Experiments in rat colon explants exposed to benzo(a)pyrene (BP) suggest that the colon can fully activate this series of carcinogens by the same pathways as those observed in other tissues. A tissue's sensitivity to a carcinogen is related to its capacity to activate the carcinogen (although the site of metabolic activation is not necessarily the site of tumorigenesis) and its capacity to repair DNA damage induced by that chemical. To a certain extent, the known inhibitors of carcinogenesis can be divided into two groups. Some inhibitors cause 'phase 2' detoxification (essentially, conjugation) reactions; they alter the metabolism of the mixed function oxidase (MFO) system but do not increase its activity. In the case of B P, the effect of a 'phase 2'-active inhibitor is to reduce the formation of the ultimate carcinogen. The other inhibitors of carcinogenesis, for which beta-naphthoflavone is a prototype, caused both 'phase I' and 'phase 2' reactions. MFO activity is enhanced. These agents simultaneously induce oxidative reactions (often leading to activation of the carcinogen) and enhanced detoxification reactions. The net result in most cases is protection of the host against the carcinogen. (8 Refs)

MODIFICATION OF CARCINOGENESIS BY HORMONAL OR GENETIC FACTORS

14. THE ROLE OF OVARIAN STEROID HORMONES IN MAMMARY CARCINOGENESIS.

Dao TL, Henderson BE, Welsch CW, Moon, Cole, Segaloff, Sirbascu, Zumoff BJ
Dept. Breast Surgery and Breast Cancer Res. Unit, Roswell Park Memorial Inst., Buffalo, NY, 14263
Banbury Rep; 8:281-298 1981

The role of ovarian steroid hormones on the pathogenesis of mammary cancer in both in vivo and in vitro is described. Induction of mammary cancer by ovarian hormones was studied, and the following experiments were performed: castration related to induction of mammary carcinogenesis in rats (female and male), and induction of mammary tumors by local application of the carcinogen. Studies on relationship between prolactin and estrogen in mammary tumor growth and in vitro studies of mammary carcinogenesis are presented. (19 Refs)

15. INFLUENCE OF PREGNANCY AND LACTATION ON EXPERIMENTAL MAMMARY CARCINOGENESIS.

Moon RC, Shellabarger CJ, Henderson BE, Pike MC, Dao TL, Meites J, Siaba YN
Life Sciences Div., IIT Res. Inst., Chicago, IL, 60616
Banbury Rep; 8:352-364 1981

The influence of pregnancy and lactation on experimental mammary carcinogenesis (MC) was studied in Sprague-Dawley female rats; 7,12-dimethylbenz(a)anthracene (DMBA)-induced MC in the rat is influenced by parity. The effect of age at which the first litter is borne on DMBA-induced MC, when MC is initiated at a subsequent period in the life of the animal, was examined. The age at which pregnancy ensues did not appear critical in the rat. Tumor hormone responsiveness in primiparous rats appears related to the age at which pregnancy occurs; pregnancy may alter the sensitivity of mammary cells to stimulatory hormones. (19 Refs)

16. PROLACTIN AND GROWTH HORMONE IN THE DEVELOPMENT, PROGRESSION, AND GROWTH OF MURINE MAMMARY TUMORS.

Welsch CW
Dept. Anatomy, Michigan State Univ., East Lansing, MI, 48824
Banbury Rep; 8:299-315 1981

The role of prolactin and growth hormone in the development and growth of spontaneous rodent mammary tumors, were examined. Growth of transplantable rodent mammary tumors, and development and growth of carcinogen-induced rat mammary tumors were also examined. Prolactin is important in initiating and promoting phases of murine mammary tumorigenesis, while the role of growth hormone appears to be less important. The role of growth hormone in the oncogenesis remains to be determined. (72 Refs)

17. PITUITARY AND STEROID HORMONES IN RADIATION-INDUCED MAMMARY TUMORS.

Shellabarger CJ
Medical Dept., Brookhaven National Lab., Upton, NY, 11973
Banbury Rep; 8:339-351 1981

Advantages of the radiation-induced (RI) rat mammary tumor system as a mode for studying RI breast cancer in humans and the rat mammary fibroadenoma response to irradiation are discussed. Evidence for chemically induced carcinogenesis and RI carcinogenesis is compared. Estrogen synergism in mammary carcinogenesis is reviewed; women whose cancer is 'initiated' may develop breast cancer if the disease is 'promoted,' even if the promotion occurs years after initiation. (57 Refs)

18. THE INFLUENCE OF ANDROGENS, ANTI-ANDROGENS, AND CASTRATION ON CELL PROLIFERATION IN THE JEJUNAL AND COLONIC CRYPT EPITHELIA, AND IN DIMETHYLHYDRAZINE-INDUCED ADENOCARCINOMA OF RAT COLON.

Tutton PJ, Barkla DH
Dept. Anatomy, Monash Univ., Clayton, 3168, Australia
Virchows Arch [Cell Pathol]; 38(3):351-355 1982

Androgenic hormones have previously been shown to promote cell proliferation in the small intestine of rat and androgen receptors have been demonstrated in carcinomata of the large intestine of rat. In this study the influence of testosterone and of castration on epithelial cell proliferation in the small intestine, the large intestine and in dimethylhydrazine-induced colonic tumors is compared. Cell proliferation in the small intestine and in colonic tumors was accelerated by testosterone treatment, and cell proliferation in colonic tumors, but not in the small intestine, was retarded following castration. Cell proliferation in colonic tumors was also inhibited by the anti-androgenic drug, Flutamide. Testosterone and castration each failed to influence cell proliferation in the colonic crypt epithelium of both normal and carcinogen-treated animals. (Author abstract) (22 Refs)

OTHER STUDIES OF THE MODIFICATON OF CARCINOGENESIS

19. ENHANCEMENT OF AFLATOXIN B1 INDUCED LIVER CARCINOGENESIS BY PORTAL DIVERSION IN THE RAT.

Franco D, Morin J, Szekely AM, Bismuth H
Departement de Recherche Chirurgicale, Universite Paris-Sud, Hopital Paul-Brousse, 14, Avenue Paul-Vaillant-Couturier, 94800 Villejuif, Cedex, France
Biomedicine [Express]; 35(5):162-165 1981

Conflicting results have been reported on the influence of portacaval anastomosis on liver carcinogenesis. The purpose of this investigation was a study the effect of portal diversion on liver carcinogenesis induced in the rat by a potent chemical liver carcinogen, Aflatoxin B1 (AFB1). Liver tumors appeared earlier and were significantly bigger in rats with shunts than in sham-operated controls. Portal diversion also induced in rats fed AFB1 a splenic atrophy with nearly complete disappearance of Malpighian corpuscles suggesting a profound immunodepression. This might be responsible for the enhancement of liver cancer by portacaval anastomosis in the rats fed AFB1. Thus, the influence of portal diversion on liver cancers appears to be multifactorial. (Author abstract) (12 Refs)

STUDIES OF TUMOR PROMOTION OR COCARCINOGENESIS IN MOUSE SKIN

20. COMPARISON OF THE EFFECTS OF 3-ISOBUTYL-1-METHYLXANTHINE AND ADENOSINE CYCLIC 3':5'-MONOPHOSPHATE ON THE INDUCTION OF SKIN TUMORS BY THE INITIATION-PROMOTION PROTOCOL AND BY THE COMPLETE CARCINOGENESIS PROCESS.

Perchellet JP, Boutwell RK
McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI, 53706
Carcinogenesis; 3(1):53-60 1982

Topical application of either 5 umol of 3-isobutyl-1-methylxanthine (IBMX) or 0.25 umol of adenosine cyclic 3':5'-monophosphate (cyclic AMP) to the initiated skin of the mouse prior to each promotion with 8.5 nmol of 12-O-tetradecanoylphorbol-13-acetate (TPA) inhibited the formation of papillomas and carcinomas. Combined treatments including IBMX and cyclic AMP caused additive reduction of the incidence of skin papillomas and carcinomas promoted by TPA. A good correlation was observed between the reduction of the tumor incidence by IBMX and cyclic AMP and their inhibition of TPA-stimulated polyamine, RNA, protein, and DNA syn-

thesis. Since repeated treatments with these agents before or after initiation with a single subcarcinogenic dose of 7,12-dimethylbenz[a]anthracene (DMBA) did not alter significantly the development of skin tumors, the present results suggest that, in the two-step initiation-promotion protocol, both IBMX and cyclic AMP treatments may decrease specifically the promoting stimulus of skin carcinogenesis. The same doses of IBMX and cyclic AMP inhibited the accumulation of polyamines and the increase in macromolecular synthesis observed in DMBA-treated skin, but their effect on DMBA-induced skin carcinogenesis was dependent upon the protocol used and the dose of carcinogen applied. IBMX and cyclic AMP treatments failed to inhibit the induction of skin tumors by weekly applications of 0.2 umol of DMBA. In contrast to the inhibitor inhibitory effect of cyclic AMP treatment, IBMX enhanced the carcinogenic response to a single topical application of 3.6 umol of DMBA. The opposite effects of these agents on the carcinogenicity of DMBA correlated well with their different alteration of DMBA-induced unscheduled DNA synthesis in vitro. Cyclic AMP (0.5 mM) enhanced, whereas IBMX (0.5 mM) inhibited, the DMBA-induced incorporation of labeled precursor into DNA of isolated epidermal cells during incubation in the presence of hydroxyurea. Therefore, it is suggested that the different modulation of DMBA carcinogenesis by IBMX and cyclic AMP may result from concomitant effects o n both the initiating and promoting components of the carcinogen. (Author abstract) (41 Refs)

21. TWO-STAGE SKIN CARCINOGENESIS IN SENSITIVE AND RESISTANT MOUSE STRAINS.

Ashman LK, Murray AW, Cook MG, Kotlarski I
Dept. Microbiology and Immunology, Univ. Adelaide, G.P.O. Box 498, Adelaide 5001, Australia
Carcinogenesis; 3(1):99-102 1982

Strains of laboratory mice vary markedly in their susceptibility to two-stage skin carcinogenesis using 7,12-dimethylbenz[a]anthracene (DMBA) as the initiating carcinogen and croton oil as promoter. This study has been undertaken in order to clarify the basis of the strain differences. LACA mice were used as the susceptible strain and BALB/c mice as the resistant strain. DMBA was a more effective complete carcinogen in LACA mice than in BALB/c mice. However, dose-response studies with respect to DMBA in the two strains in two-stage carcinogenesis suggested that metabolic activation of DMBA to the active carcinogen was not limiting in the resistant strain. The observed strain differences in response to DMBA in one and two stage carcinogenesis may reflect the ability of DMBA to also act as a promoter in the two strains. The possibility that the strains vary in their ability to repair damaged DNA has, however, not been eliminated. Unlike polycyclic aromatic hydrocarbon carcinogens such as DMBA, phorbol ester promoters (the active components in croton oil) do not appear to require metabolic activation. However, they are degraded and inactivated by epidermal and other cells. Experiments in which the dose and frequency of application of croton oil were increased, and the unrelated promoter anthralin was substituted for croton oil, failed to produce any evidence that differences in promoter degradation contributed to the differences in susceptibility between strains. (Author abstract) (12 Refs)

22. HAIRLESS MOUSE SKIN IN TWO-STAGE CHEMICAL CARCINOGENESIS. AN EXPERIMENTAL STUDY WITH SPECIAL REFERENCE TO CELL KINETICS, PAPILLOMA REGRESSION AND THE POSSIBLE DEVELOPMENT OF INCREASED CELLULAR RESISTANCE.

Iversen OH
Inst. Pathology, Univ. Oslo, Rikshospitalet, Oslo 1, Norway
Virchows Arch [Cell Pathol]; 38(3):263-272 1982

Hairless mice of the hr/hr Oslo strain were initiated by a topical skin application of 51.2 ug DMBA and thereafter treated by twice weekly applications of 17 nmol TPA. Papilloma development, the rate of papilloma regression and some cell kinetic parameters were studied. Papillomas were produced from wk 7 at an av rate of 0.33 tumors per animal per wk. This rate fluctuated from an initial rate of 0.53, which flattened off to 0.16 when TPA treatment was stopped for a period, and increased again to 0.34 when TPA applications were resumed. The treatment led to the development of hyperplasia, which was quantitated, and was most pronounced after 7 wk of promotion. Thereafter the hyperplasia dwindled. During TPA treatment a considerable reduction of epidermal turnover time was observed. After 8 wk of such treatment the turnover time of the epidermis was 24 h as compared with a normal time of 200 h. At the end of the treatment the turnover time increased again to about 50 h. Papilloma regression occurred frequently, but the rate at which this occurred slowed down after many wk of promotion. The mechanisms underlying regression are unknown, but are probably complex: a high cellular turnover rate, vascular catastrophes, scratching, fighting, eating by other animals and immune mechanisms may all be involved. Epidermal cells seem to develop increased resistance to the toxic effects of TPA during the treatment period. It is concluded that the skin of hairless mice reacts in the same way as that of sensitive mice with hair to the two-stage treatment protocol. (Author abstract) (24 Refs)

CELL CULTURE STUDIES OF MECHANISMS OF MODIFICATION

23. SOME ASPECTS OF IN VITRO CARCINOGENESIS USING SYRIAN HAMSTER CELLS.

Umeda M, Enaka K
Tissue Culture Lab., Yokohama City Univ. Sch. Medicine, Urafune-cho 2-33, Minami-ku, Yokohama 232, Japan
Gann Monogr Cancer Res; 27:183-194 1982

Various Syrian hamster cell lots were surveyed in order to establish reliable methods for transformation in culture. Growth of cells which were suitable for transformation experiments was stimulated by treatment with 12-O-tetradecanoylphorbol-13-acetate (TPA). Suitable cells showed low cell density in control cultures and high cell density in TPA-treated cultures. Cells with a capacity for abundant growth were collected by centrifugation on bovine serum albumin discontinuous density gradient. Cells with high multiplication capacity could be collected in fractions at higher density and the cells that sedimented at higher density might be a good source for transformation experiments. Establishment of a cell line likely to have characteristics of contact inhibition of growth, P-TPA cell line, is reported. Of five clones obtained, clone 54 cells exhibited a response of cell growth to TPA stimulation and low cell density in the confluent culture. Clone 54 cells had charac-

teristics similar to those of BALB/3T3 or C3H10T1/2 cells, known to have normal growth characteristics and the capacity to be transformed by carcinogenic stimuli. P-TPA clone 54 cells responded to carcinogens and formed transformed foci. Spontaneous transformation occurred in cells cultured for more than the 20th culture generation. (23 Refs)

24. REVERSAL OF THE PROMOTIONAL EFFECT OF 12-O-TETRA-DECANOYLPHORBOL-13-ACETATE ON MORPHOLOGICAL TRANSFORMATION OF HAMSTER EMBRYO CELLS BY GLUCOCORTICOIDS.

Rivedal E
Norwegian Radium Hosp., Montebello, Oslo 3, Norway
Cancer Lett; 15(2):105-113 1982

Effects of glucocorticoids and cholesterol on morphologic transformation by benzo(a)pyrene (BP) and 12-O-tetradecanoylphorbol-13-acetate (TPA) in hamster embryo cells were studied. Cells exposed to BP (0.05 ug/ml) during the first 3 days of incubation (period 1) and then to TPA (0.05 ug/ml) during the last 3 days (period 2) had a transformation frequency of 10.2%. When present during period 2, hydrocortisone and dexamethasone strongly inhibited the formation of transformed colonies. Corticosterone had only a slight inhibitory activity and cortisone had no inhibitory activity when administered in concentrations up to 25 uM. Dexamethasone, the most potent glucocorticoid, reduced transformation frequency by greater than 50% at 0.25 nanoM and completely abolished transformation at 250 nanoM. Cholesterol (2.5 or 25 uM) increased transformation frequency. The glucocorticoids had no effect when present only during period 1. The fact that addition of dexamethasone (250 nanoM) reduced transformation frequency even when added 6 hr before staining suggested that glucocorticoids rapidly reverse the morphology of transformed colonies back to normal. (31 Refs)

25. DIESEL-EXHAUST-PARTICLE EXTRACT ENHANCEMENT OF CHEMICAL-INDUCED MUTAGENESIS IN CULTURED CHINESE HAMSTER OVARY CELLS: POSSIBLE INTERACTION OF DIESEL EXHAUST WITH ENVIRONMENTAL CARCINOGENS.

Li AP, Royer RE
Inhalation Toxicology Res. Inst., Lovelace Biomedical and Environmental Res. Inst., P. O. Box 5890, Albuquerque, NM
Mutat Res; 103(3-6):349-355 1982

Dichloromethane extracts of exhaust particles (EP) filtered from the exhaust of diesel passenger cars of five different manufacturers were tested in combination with known mutagens using the Chinese hamster ovary (CHO) hypoxanthine-guanine phosphorylase assay. N-Methyl-N'-nitro-N-nitrosoguanidine (MNNG: 0.5 ug/ml) and benzo(a)pyrene [B(a)P: 0.5 ug/ml] were administered with and without diesel EP extract (60 ug/ml in dimethyl sulfoxide) to CHO cells grown with and without Aroclor 1254-induced rat-liver S9 activator. Mutagenicity of the EP extract alone was uniformly low, but treatment of CHO cells with mutagen plus EP extract consistently yielded a mutant frequency higher than expected. Without S9 activation, combined treatment of EP + MNNG gave a mutant frequency 1.4-1.9 x higher than expected. With S9 activation the EP + B(a)P treatments resulted in an observed mutation frequency 2.8-3.2 x the expected value. The observed enhancement phenomenon is highly reproducible, and also affects sister-chromatid exchanges and mutation to ouabain resistance. (21 Refs)

26. EFFECTS OF 12-O-TETRADECANOYL-PHORBOL-13-ACETATE ON CELL PROLIFERATION AND EPSTEIN-BARR VIRUS DNA REPLICATION.

Lin JC, Smith MC, Pagano JS
Cancer Res. Center, Dept. Biochemistry and Nutrition, Sch. Medicine, Univ. North Carolina, Box 3, Swing Building, 217H, Chapel Hill, NC, 27514
Virology; 117(1):186-194 1982

The effect of a tumor promoter, 12-O-tetradecanoyl-phorbol-13-acetate (TPA), on cell growth and replication of Epstein-Barr virus DNA in Burkitt's lymphoma cell lines and in a Burkitt somatic hybrid cell line (D98/HR-1) were studied. Following TPA treatment, cell proliferation was inhibited in all cell lines tested. The degree of inhibition of cell proliferation was greater if the cells were in a quiescent stationary phase (analogous to the G0 stage) than if the cells were in a steady-state mode of exponential growth when TPA was added. Induction of Epstein-Barr virus (EBV) DNA replication was observed only in P3HR-1 and D98/HR-1 cells, but not in Raji cells similarly exposed to TPA, as determined by cRNA-DNA hybridization with EBV-specific cRNA probe. Transient exposure (24 hr) of P3HR-1 cells to TPA followed by subsequent washing and incubation in TPA-free medium resulted in an increase (sixfold) in EBV genome copies per cell to the same level as achieved with continuous treatment; the increases in viral genome copies paralleled the increase in [3H]thymidine incorporation into EBV DNA. With transient TPA exposure, there was a 2-day lag period in cell proliferation and thereafter followed the similar kinetics of cell proliferation as those of the nontreated cells. These results indicate that transient exposure to TPA is sufficient to trigger the cells to enter the EBV replicative cycle, and the inhibition of some step in cell proliferation during the lag period may be inextricably linked to the effect of TPA in viral induction. (Author abstract) (36 Refs)

27. EFFECTS OF PHORBOL ESTERS ON FETAL RAT EPIDERMAL CELLS IN CULTURE.

Indo K, Miyaji H
Dept. Pathology, Hyogo Coll. Medicine, Mukogawa-cho 1-1, Nishinomiya 663, Japan
Gann Monogr Cancer Res; 27:145-158 1982

Effects of 12-O-tetradecanoyl-phorbol-13-acetate (TPA) on aneuploid nonmalignant fetal rat epidermal cells (FRSK-2 cells) were investigated. TPA inhibited cell proliferation at concentrations above 1 nanog/ml, while a stimulating effect was noted at concentrations of 0.01-0.1 nanog/ml after 24 hr. The inhibitory effect continued at 72 and 120 hr, while the stimulatory effect at low concentrations was not observed. TPA inhibited keratinization of lamellar processes of many aneuploid premalignant epidermal cell lines, but did not inhibit keratinization of malignant epidermal cell but destroyed the polarity retained in their keratinization processes. Two-stage treatment of FRSK-2 cells with benzo[a]pyrene (BP; 1 ug/ml for 1, 2, 7, or 14 days), then maintained in TPA-containing medium (1, 10, 100, and 1,000 nanog/ml) for 10 wk is reported. BP treatment for up to 2 wk did not induce any noticeable changes in the cells. However, BP treatment for 2 wk at 1 ug/ml resulted in stimulation of keratinization. TPA treatment severely inhibited the growth of FRSK-2 cells, even after BP treatment. Atypical cells were observed at 14-62 days after the beginning of TPA treatment. The changes induced in FRSK-2 cells by the two-stage treatment were irreversible. TPA treatment increased the plating efficiency of BP-treated cells. Following treatment with BP and TPA, the major characteristics of the cells included shortened generation time, acquisition of

high plating efficiency values, and abnormal keratinization processes and growth on the agar surface; comparable with changes accompanying malignant transformation of fetal rat epidermal cells. (50 Refs)

28. INDUCTION OF DIFFERENTIATION OF HUMAN PROMYELOCYTIC LEUKEMIA (HL-60) CELLS BY TELEOCIDIN AND PHORBOL-12-MYRISTATE-13-ACETATE.

Huberman E, Brasiawsky GR, Callaham M, Fugiki H
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Carcinogenesis; 3(1):111-114 1982

Human promyelocytic leukemia cells (HL-60) were induced to differentiate into macrophage-like cells in a dose-dependent manner by the tumor promoters phorbol-12-myristate-13-acetate and teleocidin, a non-phorbol ester promoter. An HL-60 cell variant, designated as R-59, which is resistant to differentiation induction by phorbol-12-myristate-13-acetate was also resistant to differentiation induction by teleocidin. Differentiation was determined by increases in the percent of morphologically mature cells and in lysozyme and nonspecific esterase activities. Both compounds inhibited the growth of HL-60 cells by blocking them from entering the synthesis phase of the cell cycle with an accumulation of cells after 48 hr in G1 phase. No such effects were observed in the R-59 cells. They were, however, as susceptible as the parent HL-60 cells, to inducers which are not considered to be tumor promoters such as dimethylsulfoxide and retinoic acid. However, these inducers cause the HL-60 and R-59 cells to differentiate into granulocyte-like cells. These results indicate that teleocidin produces in both the HL-60 and R-59 cells effects which are similar to those caused by phorbol-12-myristate-13-acetate. The possibility that agents producing such effects in these two cell types may represent potential tumor promoters is discussed. (Author abstract) (28 Refs)

29. INHIBITION OF BETA-ADRENERGIC STIMULATION OF LYMPHOCYTE ADENYLATE CYCLASE BY PHORBOL MYRISTATE ACETATE IS MEDIATED BY ACTIVATED MACROPHAGES.

Novogrodsky A, Patya M, Rubin AL, Stenzel KH
Rogoff-Wellcome Medical Res. Inst., Beilinson Medical Center, Petah-Tikva, Israel
Biochem Biophys Res Commun; 104(2):389-393 1981

The in vitro effect of phorbol-12-myristate-3-acetate (PMA) on isoproterenol-stimulated adenylate cyclase in human peripheral blood mononuclear cells (PBM) was investigated with radioimmuno assay for cyclic AMP. PMA inhibited the isoproterenol-stimulated adenylate cyclase system in PBM but not in purified T-cells or in membrane preparations from turkey erythrocytes. Oxygen-derived radicals produced by PMA-activated macrophages evidently caused the inhibition. (12 Refs)

30. EFFECTS OF 12-O-TETRADECANOYL-PHORBOL-13-ACETATE ON MYOFIBRIL INTEGRITY AND CA++ CONTENT IN DEVELOPING MYOTUBES.

Croop J, Dubyak G, Toyama Y, Dlugosz A, Scarpa A, Holtzer H
Dept. Anatomy, Univ. Pennsylvania, Philadelphia, PA, 19104
Dev Biol; 89(2):460-474 1982

The cocarcinogen 12-O-tetradecanoyl-phorbol-13-acetate (TPA) in chick embryo breast muscle culture caused degradation of striated myofibrils to molecules that did not bind antibodies to light meromycin. Dissolution of the striated myofibrils correlated with a failure by TPA-treated myotubes to accumulate Ca++. Reversion of the degradation processes occurred readily but required de novo protein synthesis. The normal programmed appearance of fibroblast-type 10 nano(n)m filaments and persistence of the muscle-type 10-nm filaments was not altered by TPA. Constitutive contractile proteins of presumptive myoblasts and fibroblasts and their replication were not affected by TPA. (65 Refs)

31. HEXOSE TRANSPORT IN UNDIFFERENTIATED AND DIFFERENTIATED BALB/C 3T3 PREADIPOSE CELLS: EFFECTS OF 12-O-TETRADECANOYLPHORBOL-13-ACETATE AND INSULIN.

O'Brien TG
Wistar Inst. Anatomy and Biology, Philadelphia, PA, 19104
J Cell Physiol; 110(1):63-71 1982

The hexose transport system of BALB/c 3T3 (clone A31T) cells, both before and after adipose conversion, was characterized and its modulation by 12-O-tetradecanoylphorbol-13-acetate (TPA) and insulin was studied by 14C-2-deoxyglucose (2DG) uptake and 3-O-3H-methylglucose (3MG) transport assay. TPA stimulated both 2DG uptake and 3MG transport systems in the undifferentiated cells, with the concentration stimulating half-maximal response being 3 nano (n) M for the 2DG system and 30 nM for the 3MG system. TPA also stimulated both systems in differentiated cells, but 3MG transport decayed much more rapidly than the level of 2DG upatke. Stimulation of 2DG uptake in undifferentiated cells by protein factors and TPA was as follows: TPA greater than or equal to fetal bovine serum greater than or equal to epidermal growth factor; insulin (170 nM) had no effect. Insulin did not stimulate 3MG transport in undifferentiated cells, but did activate it in differentiated cells over the range 1.7 nM -1.7 uM, with half-maximal response occurring at 0.17 uM; TPA was stimulatory in both types of cells, with half-maximal response at 30 nM in both. When the agents were used together insulin caused a significant additional stimulation of 3MG transport system of that caused by TPA alone. Cycloheximide treatment of differentiated cells concurrently with, or 6 h r prior to, insulin had no effect on its stimulation of 3MG transport, but did cause a 75% inhibition of the TPA-stimulated response. Long-term exposure of differentiated cells to insulin abolished the 3MG-transport acute stimulation response to insulin, but not the TPA acute response; long-term exposure to TPA did not adversely affect either TPA or insulin response in differentiated cells. Apparently TPA and insulin stimulate hexose transport in adipose cells by different mechanisms. (30 Refs)

32. IN VITRO STIMULATION OF MOUSE NK CELL ACTIVITY BY PHORBOL ESTERS: A PATHWAY DIFFERENT FROM INTERFERON-INDUCED ACTIVATION.

Kolb JP, Senik A, Castagna M
Lab. Cellular Immunology, Institut de Recherches Scientifiques sur le Cancer, B.P. No. 8, 94802 Villejuif Cedex, France
Cell Immunol; 65(2):258-271 1981

Tumor promoters of the phorbol diester type were tested in vitro for their effect on mouse natural killer (NK) activity. The 12-O-tetradecanoyl-phorbol-13-acetate (TPA) significantly increased the spontaneous cytotoxicity of spleen cells preincubated with this reagent, with a maximal effect at 10-20 ng/ml. Higher concentrations of the weak tumor promoter phorbol-12,13-dibenzoate (PDB) were required to display the same NK-enhancing property, while the inactive tumor promoter 4-

alphaphorboldidecanoate was ineffective at any concentration. TPA-responding spleen cells displayed the same characteristics as classical NK cells: they were present in nude mice, did not adhere to nylon wool, bore the Thy-1 antigen, and displayed the same target cell specificity as interferon-activated NK cells. A major difference with the interferon-induced NK activation resides in the fact that the TPA-inducible increase in lytic activity does not require RNA and protein synthesis. Our results suggest two different NK activation pathways for IFN and phorbol esters. (Author abstract) (36 Refs)

33. NEUTROPHIL ACTIVATION MONITORED BY FLOW CYTOMETRY: STIMULATION BY PHORBOL DIESTER IS AN ALL-OR-NONE EVENT.

Hafeman DG, McConnell HM, Gray JW, Dean PN
Stauffer Lab. Physical Chemistry, Stanford, CA, 94305
Science; 215(4533):673-675 1982

The population dynamics of single-cell stimulation was analyzed by monitoring autofluorescence by flow cytometry. Stimulation of the respiratory burst in human neutrophils by 12-O-tetradecanoyl phorbol-13-acetate (TPA) caused a decline in highly fluorescent cells (characteristic of resting neutrophils) and a corresponding increase in the number of weakly fluorescent cells (characteristic of activated neutrophils). Increasing concentrations of TPA caused increasing numbers of cells to shift from the highly fluorescent population to the weakly fluorescent population without the appearance of intermediate populations. Thus the neutrophil respiratory burst, a component of neutrophil cytotoxic response, is t riggered in an all-or none fashion. (Author abstract) (38 Refs)

34. DNA STRAND BREAKAGE IN HUMAN LEUKOCYTES EXPOSED TO A TUMOR PROMOTER, PHORBOL MYRISTATE ACETATE.

Birnboim HC
Health Sciences Div., Radiation Biology Branch, Atomic Energy of Canada Ltd., Chalk River, Ontario, K0J 1J0, Canada
Science; 215(4537):1247-1249 1982

The phorbol myristate acetate-stimulated respiratory burst in human peripheral blood leukocytes is associated with extensive DNA strand breakage. Damage to DNA occurs before gross cellular damage is evident and may be related to the action of phorbol myristate acetate as a skin tumor promoter in animals. (Author abstract) (16 Refs)

REVIEWS AND OTHER RELATED STUDIES

35. CHEMICAL CARCINOGENESIS AND SMOKING.

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Dept. Pathology, Univ. Toronto, Banting Inst., 100 College St., Toronto, Ontario M5G 1L5, Canada
Can J Public Health; 72(6):381-385 1981

Development of cancer in the respiratory tract in relation to some of the steps for carcinogenesis is reviewed. Metabolic activation of the majority of the known carcinogens is a prerequisite for interactions with DNA and other cellular components. Genetic defects in repair processes in cells may lead to increase in sensitivity to some carcinogenic influences, and the role of cell proliferation is important. The next step in carcinogenesis is promotion, the selective stimulation of initiated cells to grow. Suggested mechanisms of promotion are differential inhibition, stimulation, necrosis with regeneration, and recovery. Regression or maturation to normal-appearing tissue appears to be entirely dependent on the environment. Persistence of focal proliferations with a greatly increased risk for development of a second focal change is considered to be the first neoplastic step. Important component of cancer development with smoking is the promoting effect of components in the smoke. Later precancerous changes characterized by cytologic and histologic alterations show biological reversibility. Studies indicated a presence of a distinctive enzyme and other markers very early in carcinogenesis and long before any cytologic evidence of alteration appears. In the bladder, the early cells in man and in animal show chages in staining for alkaline phosphatase. The observations point to possibility of developing characteristic staining procedures that should enable the identification of early preneoplastic or premalignant changes in bronchial epithelial cells. (30 Refs)

36. BIOLOGICAL MODELS AND STATISTICAL INTERACTIONS: AN EXAMPLE FROM MULTISTAGE CARCINOGENESIS.

Siemiatycki J, Thomas DC
Epidemiology and Preventive Medicine Res. Centre, Institut Armand-Frappier, Case postale 100, Laval-des-Rapides, Quebec, Canada
Int J Epidemiol; 10(4):383-387 1981

From the assessment of statistical interaction between risk factors it is tempti ng to infer the nature of the biologic interaction between the factors. However, the use of statistical analyses of epidemiologic data to infer biologic processes can be misleading. As an example, we consider the multistage model of carcinogenesis. Under this biologic model, it is shown, by means of simple hypothetical examples, that even if carcinogenic factors act independently, some pairs may fit an additive statistical model, some a multiplicative statistical model, and some neither. The elucidation of biological interactions by means of statistical models requires the imaginative and prudent use of inductive and deductive reasoning; it cannot be done mechanically. (Author abstract) (23 Refs)

37. GASTROINTESTINAL CANCER: ENDOGENOUS FACTORS.

Bruce WR, Correa P, Lipkin M, Tannenbaum SR, Wilkins TD
Ontario Cancer Inst., Toronto, M4X 1K9, Canada
Banbury Rep 7: 468 pp., 1981.

The role of diet in cancer was examined. Sessions on gastrointestinal microbiology (microbiological considerations in experimental studies, effect of diet on human fecal flora, metabolism of xenobiotics by intestinal flora, and intestinal bacterial activity and carcinogenesis), fiber (ecology of gut fermentation in man, dietary fiber breakdown in the human colon role of fat, fiber, and other modifiers of intestinal carcinogenesis in cancer prevention), host response to carcinogens (risk factor profiles for individuals at increased risk for colon cancer, fecal mutagens and colorectal polyps, enzymes of normal, premalignant, and malignant colonic cells, role of cytochrome P-450 in colon response xenobiotics, inhibitors of gastrointestinal neoplasia, colonic activation of carcinogens), mutagens (in extracts of gastrointestinal mucosa, nitrosation in stomach mucosal tissue of humans and dogs, isolation of mutagens produced in the human colon by bacterial action, structural studies and properties of mutagens isolated from human feces, bacterial fluctuation tests of mutagenic activity in human feces, intake, formation, and release of mutagens by man), N-nitroso compounds (endogenous formation of N-nitroso compounds, analysis of

human biological specimens for nitrosamines, block nitrosamine formation using ascorbic acid and alpha-tocopherol, distribution and metabolism of nitrate and nitrite in rats, analysis of nitrate, nitrite, and nitrosamines in human feces, metabolism of nitrate), bile acids and other lipids (bile salts as tumor promoters, bile acids in colorectal carcinogenesis, and analysis of feces for benzopyrene after consumption of charcoal-broiled beef) and epidemiology and design of future studies (epidemiologic tests of hypothesis relating diet and cancer, large-scale cohort study of diet and selected digestive system cancers, and possible application of mutagenesis testing to cancer epidemiology). (716 Refs)

38. THE INDUCTION OF MUTATION AND CELL DIFFERENTIATION BY CHEMICALS WHICH INITIATE OR PROMOTE TUMOR FORMATION.

Huberman E
Div. Biological and Medical Res., Argonne Natl. Lab., Argonne, IL, 60439
Gann Monogr Cancer Res; 27:127-144 1982

Detection of tumor promoting chemicals in mammalian cell culture systems is described. Chemical carcinogens are mutagenic for mammalian cells, with their degree of mutagenicity correlating with their degree of carcinogenicity. In some cases, the metabolites responsible for mutagenesis are also responsible for initiating the carcinogenic event. A cell/organ type specificity can be established with a cell-mediated assay. The effect of tumor promoters such as the phorbol-diesters in cultured human HO melanoma and human HL-60 promyelocytic leukemia cells was studied. In both HO and HL-60 cells, the ability of ten different phorbol esters to induce differentiation correlated with their tumor-promoting activity in mouse skin. Changes in polyamine levels may involve biological pathways other than the known biosynthetic ones and these pathways or their by-products may be involved in the control of cell growth and differentiation in HL-60 cells. Studies of specific binding of 20-[3H]-phorbol 12,13-dibutyrate (PDBu) in HL-60 cells demonstrated that down regulation of specific PDBu binding is an important phenomenon involved in the mechanism of action of phorbol esters and may lead to modification of various biological and biochemical events involved in cellular differentiation and perhaps tumor promotion. Human HO melanoma and HL-60 leukemia cells may be useful for studying the mode of action of known tumor promoters and in the identification of some unknown classes of tumor-promoting agents. (82 Refs)

39. THE USE OF MAMMALIAN CELL MUTANTS TO STUDY THE MECHANISMS OF CARCINOGENESIS.

Trosko JE, Chang CC, Warren ST, Liu PK, Wade MH, Tsushimoto G
Dept. Pediatrics and Human Development, Michigan State Univ., Coll. Human Medicine, East Lansing, MI, 48824
Gann Monogr Cancer Res; 27:159-179 1982

Use of mammalian cell mutants to study the mechanisms of carcinogenesis is reviewed. A genetic approach was used to study molecular mechanisms of initiation and promotion. It was shown that different mutagens induce different types of mutations and that phenotypic expression is influenced by tumor promoters or antipromoters, while mutation fixation is not. General considerations of in vitro mutagenesis at the gene level are discussed. Study of mutagen-sensitive DNA-repair deficient mutants and xeroderma pigmentosum and Bloom's syndrome cells demonstrated that a defect in DNA repair or DNA replication may cause mutagenesis. An in vitro assay to detect tumor promoters was designed with the basic premise that all tumor promoters block metabolic cooperation. Inhibition of cell-cell communication by known tumor prom oters might be one of the initial events triggered by tumor promoters. It is possible to study the mechanism of tumor promoters and to screen for environmental promoters. An hypothesis for the relationship of metabolic cooperation and carcinogenesis is proposed. (144 Refs)

40. INITIATION AND PROMOTION, MUTAGENESIS AND TRANSFORMATION OF C3H/10T1/2 MOUSE EMBRYO FIBROBLASTS.

Heidelberger C
Univ. Southern California Sch. Medicine, Los Angeles, CA, 90031
Gann Monogr Cancer Res; 27:207-219 1982

The C3H/10T1/2 mouse embryo fibroblast cloned cell line is discussed with respect to initiation and promotion, mutagenesis, and transformation. Transformation by polycyclic aromatic hydrocarbons was dose-dependent and did not involve activation of an endogenous retrovirus or its cores or RNA. Metabolism of benzo[a]pyrene in microsomes of these cells involves formation of 7,8-and 9,10-diols, phenols and quinones. UV light is a pure initiator, x-rays initiate transformation, and saccharin in a weak promoter. While 12-O-tetradecanoyl phorbol-13-acetate (TPA) is strongly mitogenic and produces hyperplasia in mouse skin, it does not significantly increase the saturation density of C3H/10T1/2 cells. All chemical classes of tumor promoters are not suitable for screening by measuring their effects on the 5-azacytidine-induced differentiation of C3H/10T1/2 cells because of inconsistencies in results. Mutagenic and oncogenic transformation in these cells is described. Mutagenesis data can be interpreted in various ways in order to obtain the desired result. In this system mutagenesis appears to be necessary but is not sufficient for transformation. (60 Refs)

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As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. AN EVALUATION OF THE GENETIC TOXICITY OF EPICHLORHYDRIN. A REPORT OF AN EXPERT GROUP OF THE INTERNATIONAL COMMISSION FOR PROTECTION AGAINST ENVIRONMENTAL MUTAGENS AND CARCINOGENS.

Sram RJ, Tomatis L, Bridges BA, Clemmesen J
(c/o Lohman), Medical Biological Lab. TNO, P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 87(3):299-319 1981

2. ETHYLENE DIBROMIDE (EDB). (REVISED).

NIOSH Document Development Branch
Robert A. Taft Lab., National Inst. Occupational Safety and Health, 4676 Columbia Parkway, Cincinnati, OH, 45226
Curr Intell Bull NIOSH (37): 13 pp., 1981.

3. CHEMICAL CARCINOGENESIS AND SMOKING.

Farber E
Dept. Pathology, Univ. Toronto, Banting Inst., 100 College St., Toronto, Ontario M5G 1L5, Canada
Can J Public Health; 72(6):381-385 1981

RADIATION CARCINOGENESIS

4. CELLULAR TRANSFORMATION BY RADIATION: INDUCTION, PROMOTION, AND INHIBITION.

Borek C
Radiological Res. Lab., Cancer Center/Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032
J Supramol Struct Cell Biochem; 16(4):311-336 1981

5. EFFECTS OF IONIZING RADIATION ON THE DEVELOPING EMBRYO AND FETUS: A REVIEW.

Hoffman DA, Felten RP, Cyr WH
Bureau Radiological Health, Rockville, MD
Effects of Ionizing Radiation on the Developing Embryo and Fetus: A Review. Available from National Technical Information Service, Springfield, VA, as PB82-115379-, 160 pp., 1981

DIETARY FACTORS IN CARCINOGENESIS

6. BETA-CARBOLINES, PSYCHOACTIVE COMPOUNDS IN THE MAMMALIAN BODY.

Airaksinen MM, Kari I
Dept. Pharmacology, Univ. Kuopio, P.O. Box 138, SF-70101 Kuopio 10, Finland
Med Biol; 59(4):190-211 1981

7. DIET AND CANCER OF THE LARGE BOWEL.

Zaridze DG
Analytical Epidemiology Programme, Div. Epidemiology and Biostatistics, International Agency for Res. on Cancer, 150 Cours Albert Thomas, 69372 Lyon, Cedex 2, France
Nutr Cancer; 2(4):241-249 1981

8. INFLUENCE OF DIET ON MAMMARY CANCER.

Carroll KK
Dept. Biochemistry, Univ. Western Ontario, London, Ontario, N6A 5C1, Canada
Nutr Cancer; 2(4):232-236 1981

9. ARTIFICIAL SWEETENERS IN RELATION TO THE EPIDEMIOLOGY OF BLADDER CANCER.

Howe GR, Burch JD
NCI Canada Epidemiology Unit, Univ. Toronto, Ontario, Canada
Nutr Cancer; 2(4):213-216 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

10. EPIDEMIOLOGY AND THE STUDY OF CANCER.

Woods NF, Woods JS
Dept. Physiological Nursing, Sch. Nursing, Univ. Washington, Seattle, WA
Cancer Nursing. Marino LB, ed. St. Louis, The C. V. Mosby Company, 635 pp., 1981.

11. EPIDEMIOLOGY OF CUTANEOUS MALIGNANT MELANOMA.

Balda BR
Dermatologische Klinik und Poliklinik der Universitat, Frauenlobstr. 9-11, D-8000 Munchen 2, W. Germany
MMW; 123(50):1923-1926 1981
In GER

12. THE SMOKING-INDUCED EPIDEMIC.

Doll R
Green Coll. Oxford, Oxford, England
Can J Public Health; 72(6):372-381 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

13. HEALTH HAZARDS OF ASBESTOS EXPOSURE.

Kaw JL
Industrial Toxicology Res. Centre, Lucknow 226 001, India
J Sci Ind Res; 40(5):342-346 1981

14. OVERVIEW OF FINNISH EPIDEMIOLOGIC STUDIES ON OCCUPATIONAL CANCER.

Tola S
Dept. Epidemiology and Biometry, Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
Scand J Work Environ Health; 7(Suppl4):133-139 1981

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

15. ALKYLATION OF DNA AND TISSUE SPECIFICITY IN NITROSAMINE CARCINOGENESIS.

Montesano R
International Agency for Res. on Cancer, 150, Cours Albert Thomas, 69372 Lyon Cedex 2, France
J Supramol Struct Cell Biochem; 17(3):259-273 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

16. TRANSFORMATION INDUCED BY HERPES SIMPLEX VIRUS: A POTENTIALLY NOVEL TYPE OF VIRUS-CELL INTERACTION.

Hampar B
Lab. Molecular Virology, NCI, Frederick, MD, 21701
Adv Cancer Res; 35:27-47 1981

17. ONCOGENESIS BY RNA TUMOR VIRUSES.

Koyama T
Dept. Carcinostasis Res., Tokyo Univ. Medical Res. Inst., 4-6-1 Kindai, Minato-ku, Tokyo 108, Japan
Tanpakushitsu Kakusan Koso; 26(14):2121-2129 1981
In JPN

18. POLYOMA T ANTIGENS.

Eckhart W
Tumor Virology Lab., Salk Inst., San Diego, CA, 92138
Adv Cancer Res; 35:1-25 1981

METHODOLOGY IN CARCINOGENESIS RESEARCH

19. EPIDEMIOLOGICAL ASSESSMENT OF DIETARY INTAKE.

James WP, Bingham SA, Cole TJ
Medical Res. Council's Dunn Clinical Nutrition Center, Adenbrooke's Hosp., Cambridge, England
Nutr Cancer; 2(4):203-212 1981

20. ASSESSMENT OF TECHNOLOGIES FOR DETERMINING CANCER RISKS FROM THE ENVIRONMENT.

Office of Technology Assessment
Office of Technology Assessment, Washington, DC
Assessment of Technologies for Determining Cancer Risks from the Environment. Available from National Technical Information Service, Springfield, VA, as PB81-235400-, 243 pp., 1981.

21. ANTIBODIES SPECIFIC FOR DNA COMPONENTS STRUCTURALLY MODIFIED BY CHEMICAL CARCINOGENS.

Muller R, Rajewsky MF
(c/o Rajewsky) Institut fur Zellbiologie (Tumorforschung), Universitat Essen (GH), Hufelandstrasse 55, Essen 1, W. Germany
J Cancer Res Clin Oncol; 102(2):99-113 1981

22. APPLICATION OF THE MICROBIAL MUTATION TEST IN OCCUPATIONAL HEALTH AND ITS FUTURE PROBLEMS.

Takemura N
Dept. Public Health, Jikei Univ., 25-8, Nishi-Shimbashi 2-chome, Minato-ku, Tokyo, 105, Japan
Sangyo Igaku; 23(4):355-365 1981
In JPN

OTHER REVIEWS IN CARCINOGENESIS

23. ARACHIDONIC ACID TRANSFORMATION AND TUMOR PRODUCTION.

Levine L
Dept. Biochemistry, Brandeis Univ., Walth[illegible]
Adv Cancer Res; 35:49-79 1981

24. POLYAMINES IN MAMMALIAN TUMORS PART I.

Scalabrino G, Ferioli ME
Inst. General Pathology, Univ. Milan, 20133 Milan, Italy
Adv Cancer Res; 35:151-268 1981

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MODIFICATION OF CARCINOGENESIS BY CHEMICAL AGENTS OR IRRADIATION

1. INHIBITION OF METHYLAZOXYMETHANOL-INDUCED INTESTINAL TUMORS IN THE RAT BY PYRAZOLE WITH PARADOXICAL EFFECTS ON SKIN AND KIDNEY.

Notman J, Tan QH, Zedeck MS
(c/o Zedeck), Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Cancer Res; 42(5):1774-1780 1932

Methylazoxymethanol is a potent carcinogen and induces tumors predominantly of the small intestine and colon following a single injection. Previous data indicated that alcohol dehydrogenase could convert this carcinogen to a reactive alkylating agent. Rats were treated with an inhibitor of this enzyme, pyrazole, 2 hr prior to their receiving the carcinogen. The development of intestinal and colonic tumors was prevented. The rats did, however, develop numerous tumors of the skin and kidney. Analyses of the complete autopsies are presented. The data indicate that intestinal and colonic alcohol dehydrogenase plays a role in the tumorigenic effects of methylazoxymethanol and that other non-pyrazole-sensitive enzymes exist in other organs that can also activate this carcinogen. (Author abstract) (21 Refs)

2. NEOPLASTIC LESIONS IN THE URINARY TRACT OF WISTAR RATS AFTER TREATMENT WITH N-METHYL-N-NITROSOUREA (MNU) AND ARTIFICIAL SWEETENERS.

Soudah B, Green U, Schneider P, Althoff J
Dept. Experimental Pathology, Medizinische Hochschule, Karl-Wiechert-Alle 9, D-3000 Hannover G1, W. Germany
Exp Pathol; 20(4):197-202 1981

The tumor promoting effect of saccharin, sodium cyclamate or calcium carbonate on urinary tract carcinogenesis initiated by N-methyl-N-nitrosourea (MNU) was investigated in female Wistar AF-Han rats. Based on findings from graded sections, neither enhancement nor promotion could be detected. (Author abstract) (13 Refs)

3. EFFECT OF ETHANOL ON VINYL CHLORIDE CARCINOGENESIS.

Radike MJ, Stemmer KL, Bingham E
Dept. Environmental Health, Kettering Lab., Univ. Cincinnati Medical Center, 3223 Eden Ave., Cincinnati, OH, 45267
Environ Health Perspect; 41:59-62 1981

The potential cocarcinogenicity of ethanol with vinyl chloride (VC) was studied in male Sprague-Dawley rats. A total of 320 rats (80 rats in each of four groups) were studied: Group 1 was exposed to VC (600 ppm, 4 hr/day, 5 days/wk for 1 yr), Group 2 was exposed to VC and ethanol (5% in water, beginning 4 wk before the start of VC exposure and continuing for life), Group 3 was exposed only to ethanol, and Group 4 was exposed only to filtered air. At 18 mo rats exposed to VC showed an av weight loss of approx 9%. At 18 mo the survival rate was 40% for Group 1, 18% for Group 2, 73% for Group 3, and 70% for Group 4. Angiosarcomas were found in 23% of Group 1, 50% of Group 2, and 0% of Groups 3 and 4. Hepatocellular carcinomas were found in 44% of Group 1, 60% of Group 2, 10% of Group 3, and 0% of Group 4. Lymphosarcomas were found in all groups but most frequently in Group 2. Endocrine tumors were found in 57 rats in Group 3, compared with 29 in Group 1, 30 in Group 2, and 8 in Group 4. Some rats developed more than one angiosarcoma or carcinoma. Results indicate that ethanol has a strong cocarcinogenic effect in rats exposed to VC. (8 Refs)

4. INTERACTIONS BETWEEN 7,12-DIMETHYLBENZ(A)ANTHRACENE (DMBA) AND REPEATED LOW-LEVEL X RADIATION IN HAMSTER CHEEK POUCH CARCINOGENESIS: DEPENDENCE ON THE RELATIVE TIMING OF DMBA AND RADIAT ION TREATMENTS.

Lurie AG
Div. Oral Radiology, Univ. Connecticut Health Center, Farmington, CT, 06032
Radiat Res; 90(1):155-164 1982

The effects of x-radiation prior to and during treatment with 7,12-dimethylbenz(a)anthracene (DMBA) on enhancement of hamster cheek pouch carcinogenesis were studied. The results were compared with those of previous studies when irradiation was administered during and after DMBA treatment. Young adult male outbred Syrian golden hamsters were assigned to one of four treatment groups: x-radiation alone (R: 20 R to head and neck per wk for 17 wk); DMBA alone (C: 0.1% in 0.05 ml mineral oil 2x/wk for 11 wk omitting wk 6); x-radiation plus mineral oil (R + MO); and x-radiation plus DMBA (R + C). DMBA or MO were applied topically 24 hr prior to and after R; treatment began during wk 10 of irradiation and continued 3 wk beyond the end of irradiation. All animals were sacrificed 37 wk after DMBA treatments began (46 wk after the start of irradiation). No histological changes were detectable with R alone. In one study, preirradiation may have reduced the carcinogenic effect of DMBA, while in the second study, no significant differences between the R + C group and the C group were detected. Thus, repeated exposure to low-level head and neck irradiation prior to and during DMBA treatment had little or no effect on incidence, latent period, or size of tumors induced by DMBA treatment alone. The relative timing of DMBA and x-ray treatments may be important in determining whether such treatment will interact and produce more tumors than DMBA alone; a period of x-ray/chemical treatment overlap may be necessary for enhancement. (36 Refs)

5. PROLIFERATIVE AND MORPHOLOGICAL CHANGES IN THE PULMONARY EPITHELIUM OF THE SYRIAN GOLDEN HAMSTER DURING CARCINOGENESIS INITIATED BY 210POALPHA ALPHA-RADIATION.

Shami SG, Thibodeau LA, Kennedy AR, Little JB
Inhalation Toxicology Res. Inst., Lovelace Biomedical and Environmental Res. Inst., P.O. Box 5890n Ave., Albuquerque, NM, 87185
Cancer Res; 42(4):1405-1411 1982

The role of cellular proliferation in a two-stage model of carcinogenesis in the hamster lung was investigated. Syrian golden hamsters were treated intratracheally with either one instillation of 0.2 uCi of 210Po (Po-O group), seven weekly instillations of BP (O-BP group), or 0.2 uCi 210Po followed 15 wk later by either seven instillations of 0.9% NaCl solution (Po-Sal group) or seven instillations of BP (Po-BP group). All BP instillations were 3 mg each of BP:ferric oxide (1:1, w/w) carrier particles. Serial sacrifices were performed for up to 85 wk. Two hr before sacrifice, each animal was given ip injections of 200 uCi of [3H]thymidine. Glycol methacrylate section autoradiographs (1 um) were prepared. Labeling indices in the alveolar region, labeling of terminal bronchiolar cells, and mor-

phological chang es were examined. Equal numbers of Po-Sal and Po-BP animals developed lung tumors. No tumors were found in Po-O or O-BP animals. Tumor development was preceded by the appearance of hyperplastic areas of bronchiolar-type cells in the alveolar region and by changes in morphology of bronchiolar cells. Labeling indices in the alveolar region of the treated groups were slightly increased relative to untreated controls. Labeling of terminal bronchiolar cells was highest in the Po-BP and O-BP groups and was associated with much inflammation. A single 0.9% NaCl solution instillation also increased proliferation of bronchiolar cells. We conclude that 0.9% NaCl solution instillations may potentiate carcinogenesis in the hamster lung by acting as a nonspecific stimulus to proliferation; in addition, we conclude that not all hyperplasia progressed on to form lung tumors in the Po-BP and Po-Sal groups. (Author abstract) (50 Refs)

MODIFICATION OF CARCINOGENESIS BY DIETARY COMPONENTS OR DIGESTIVE FACTORS

6. INTERACTION OF DIETARY FAT AND THE THYMUS IN THE INDUCTION OF MAMMARY TUMORS BY 7,12-DIMETHYLBENZ(A)ANTHRACENE.

Wagner DA, Naylor PH, Kim U, Shea W, Ip C, Ip MM
(c/o M. Ip) Dept. Experimental Therapeutics, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Cancer Res; 42(4):1266-1273 1982

The interaction of dietary fat and the thymus in the induction of mammary tumors by dimethylbenz(a)anthracene has been examined in female Sprague-Dawley rats. In these experiments, rats fed diets of 0.5% (low fat), 5% (normal fat), or 20% (high fat) corn oil from weaning (21 days of age) were thymectomized or sham thymectomized at 35 days of age and were given 5 mg of dimethylbenz(a)anthracene at 55 days of age. Thymectomy exerted a protective effect in rats fed low and normal fat diets, and this was not reversed by Thymosin Fraction V. In high fat-fed rats, tumorigenesis was increased compared to the low fat groups, and in addition, the protective effect of thymectomy was absent. This differential effect of thymectomy could not be explained on the basis of changes in prolactin concentration, since prolactin levels were decreased in all dietary groups. Neither diet nor thymectomy affected corticosterone levels or the estrus cycle of mature rats. Peripheral blood lymphocytes were, however, decreased by both thymectomy and increasing the fat content of the diet. It is hypothesized that the promoting effect of dietary fat on dimethylbenz(a)anthracene-induced mammary tumorigenesis is mediated via the immune system, although a role for the endocrine system still cannot be ruled out. (Author abstract) (66 Refs)

MODIFICATION OF CARCINOGENESIS BY HORMONAL OR GENETIC FACTORS

7. ROLE OF ESTROGENS AS PROMOTERS OF HEPATIC NEOPLASIA.

Wanless IR, Medline A
Dept. Pathology, Toronto Western Hosp., Toronto, Ontario, Canada
Lab Invest; 46(3):313-320 1982

The administration of estrogens to humans has been associated with the development of benign and possibly malignant hepatocellular neoplasms. This study was designed to investigate the mechanism of this association. We present a rat model that demonstrates that stilbestrol (DES) and ethinyl estradiol promote the development of hepatic neoplasms in rats previously initiated with diethylnitrosamine (DEN). Eighty male and 12 female Fischer-344 rats were given a single intraperitoneal injection of either DEN (200 mg/kg of body wt) or saline. Beginning 4 wk after injection, the rats were given an estrogen or corn oil twice weekly for up to 50 wk. Treatments were stopped at the time of sacrifice or 11 to 29 wk prior to sacrifice. Estrogen treatments included high dose DES (5 mg per dose), low dose DES (0.5 mg per dose), and ethinyl estradiol (0.2 mg per dose). Male and female rats given both DEN and high dose of DES developed grossly visible hepatic hyperplasic nodules (mean, 9.1 per liver) after 20 wk of DES. Nodules also developed if the onset of DES treatment was delayed until 28 wk after initiation. Rats given DEN alone or DES alone did not develop nodules after 20 wk. Microscopic hyperplastic foci also developed in rats given DEN plus DES, DES alone, and DEN alone. The foci in rats given DES alone were largely reversible on cessation of estrogen therapy. Mitotic activity in foci and nodules was prominent during estrogen therapy but declined markedly after cessation of therapy. Similar promoting activity of ethinyl estradiol was observed. Low dose DES was not effective in promoting tumor formation. The data indicate that estrogens promote hepatic neoplasia, perhaps by increasing hepatocyte mitotic activity and thereby facilitating the evolution of previously initiated cells into neoplastic clones. Comparison with human disease should be made with caution, especially because the estrogenic dose administered was approx 200-fold the usual contraceptive dose in humans. However, the analogy between this model and the development of human oral contraceptive-associated hepatic tumors is evident. It is possible that some women have latent 'initiated' cells that divide faster than the surrounding hepatocytes in response to estrogens. (Author abstract) (29 Refs)

8. CHANGES IN ESTROGEN RECEPTOR LEVELS DURING DES-INDUCED HEPATOCARCINOGENESIS IN THE SYRIAN HAMSTER FED ALPHA-NAPHTHOFLAVONE.

Li SA, Li JJ
Medical Res. Lab., Veterans Admin. Medical Center, Minneapolis, MN, 55417
J Steroid Biochem; 15:387-392 1981

Incidence of hepatocarcinogenesis was investigated in diethylstilbestrol (DES)-treated castrated and ovariectomized Syrian golden hamsters fed 0.2% alpha-naphthoflavone (ANF) in the diet. Induction of liver tumors (LT) by DES was essentially nil. When similar DES-treated castrated male hamsters were maintained on a diet containing ANF, nearly 70% developed LT. No LT were found in hamsters treated with ANF alone. Diet containing beta-naphthoflavone alone, or in the presence of DES did not induce LT. Competition with 250-fold excess

nonlabeled DES for tritiated estradiol (ED) binding indicated that only the 8S moiety of estrogen receptors (ER) was specific. The specificity of ER in cytosol was indicated by minimal inhibition when either radioinert cortisol, progesterone, methyltrienolone, or triamcinolone acetonide was used at the same concentration. The binding of [3H]-ED in DES plus ANF-treated liver cytosol was saturable and of high affinity with an association constant of 0.15-1.3 x 10(9) M-1. Similar results were obtained using liver cytosol derived from untreated castrated and DES-treated hamsters. DES treatment for 3-4 mo resulted in a 2.5-fold increase in specific estrogen binding, and treatment with DES plus ANF for a similar period induced a 3.5-5-fold increase in liver ER concentration. In both treated groups when sedimented in high salt sucrose gradients, 4S nuclear binders were detected for liver ER. Cytosol-nuclear receptor translocations carried out either in the presence of nonlabeled DES or at 0-3 C exhibited little nuclear uptake of the labeled ED in all tissues examined. (37 Refs)

9. PERMISSIVE ROLE OF THE PITUITARY IN THE INDUCTION AND GROWTH OF ESTROGEN-DEPENDENT RENAL TUMORS.

Lin YC, Loring JM, Villee CA
(c/o Villee), Harvard Medical Sch., Boston, MA, 02115
Cancer Res; 42(3):1015-1019 1982

Prolonged administration of estrogen to hamsters by implanted pellets induces not only renal adenocarcinomas but also enlarges pituitaries with hyperplastic and neoplastic changes, especially in the pars intermedia. The pituitaries of the diethylstilbestrol-implanted animals weigh 90 to 150 mg; those of control animals without diethylstilbestrol pellets weigh 7 to 12 mg. Castrated male hamsters were hypophysectomized, implanted with diethylstilbestrol pellets, fed laboratory chow ad libitum, and given 5% glucose in water to drink. New pellets were implanted every 3 mo, and the animals survived for 12 to 15 mo. At autopsy, none of the animals had a tumor. Sixty-two of 65 control castrated males with the same schedule of pellet implantation developed tumors. Hypophysectomized castrated males implanted with diethylstilbestrol pellets were given daily injections of 1 ug each of follicle-stimulating hormone, luteinizing hormone, and prolactin; or with 0.9% NaCl solution. These animals survived for 12 to 15 mo, but none developed kidney tumors. Other castrated males were hypophysectomized and implanted with diethylstilbestrol pellets, and 2 mo later tumor tissues were transplanted under the kidney capsule. Eighty days later, no tumors were evident in the kidneys of these animals. Control castrated males were implanted with diethylstilbestrol pellets, and 2 mo later tumor tissue was transplanted under the kidney capsule. Between 60 and 85 days later, 13 of the 15 controls had developed renal tumors. The concentrations of circulating follicle-stimulating hormone and luteinizing hormone in animals with diethylstilbestrol implants decreased with time and, by 7 mo, were similar to those in hypophysectomized animals. The concentration of prolactin in animals with diethylstilbestrol pellets increased with time and reached twice the value in the control animals without diethylstilbestrol pellets. These studies suggest that some factor secreted by the pituitary may be involved as a promoter or a cocarcinogen in the estrogen induction of kidney tumors. (Author abstract) (19 Refs)

10. 2-BROMO-ALPHA-ERGOCRYPTINE (CB-154) AND TAMOXIFEN (ICI 46,474) INDUCED SUPPRESSION OF THE GENESIS OF MAMMARY CARCINOMAS IN FEMALE RATS TREATED WITH 7,12-DIMETHYLBENZANTHRACENE (DMBA): A COMPARISON.

Welsch CW, Goodrich-Smith M, Brown CK, Mackie D, Johnson D
Dept. Anatomy, Michigan State Univ., East Lansing, MI, 48824
Oncology; 39(2):88-92 1982

Daily treatment of female Sprague-Dawley rats with 2-bromo-alpha-ergocryptine (CB-154) (prolactin suppressor) or Tamoxifen (estrogen antagonist) for 33 days before and after 7,12-dimethylbenzanthracene (DMBA) administration reduced (p less than 0.05) the incidence of mammary carcinomas by 58 and 49%, respectively. A combination of CB-154 and Tamoxifen further reduced (p less than 0.05) mammary carcinoma incidence by an additional 50-59%. Treatment with Tamoxifen for 66 days beginning 33 days after carcinogen treatment reduced (p less than 0.05) the incidence of mammary carcinomas by 65%; CB-154 treatment, during the same time period, did not significantly effect the final yield of mammary carcinomas. Th combination of Tamoxifen and CB-154 was comparable to Tamoxifen alone in suppressing the incidence of mammary carcinomas in the latter study. These results demonstrate a substantial suppressive and synergistic effect of Tamoxifen and CB-154 in the initiating phases of mammary carcinogenesis while in the early promoting phases of this oncogenic process, short-term treatment with Tamoxifen was superior to CB-154 treatment; no synergism between these clinically important compounds was observed. (Author abstract) (27 Refs)

11. ENHANCED EFFECT OF GASTRIN ON RAT STOMACH CARCINOGENESIS INDUCED BY N-METHYL-N'-NITRO-N-NITROSOGUANIDINE.

Tahara E, Shimamoto F, Taniyama K, Ito H, Kosako Y, Sunuyoshi H
Dept. Pathology, Hiroshima Univ. Sch. Medicine, 1-2-3 Kasumi, Minami-ku, Hiroshima 734, Japan
Cancer Res; 42(5):1781-1787 1982

This study deals with the effects of gastrin on the incidence of gastric tumors in rats induced by N-methyl-N'-nitro-N-nitrosoguanidine. Inbred Basel-Wistar rats received N-methyl -N'-nitro-N-nitrosoguanidine in drinking water (50 ug/ml for 32 wk) in order to produce gastric carcinoids. A treatment with sc injection of pentagastrin (300 ug/kg, once daily for 4 wk) was started at the beginning of N-methyl-N'-nitro-N-nitrosoguanidine treatment simultaneously, on the 4th, 8th, 16th, and 32nd wk after start of N-methyl-N'-nitro-N-nitrosoguanidine treatment, respectively. At autopsy, from the 55th to 60th wk after start of the experiment, only in the 8th-wk group of gastrin-treated rats was the incidence of gastric carcinoid significantly higher than in the gastrin-untreated group of rats receiving N-methyl-N'-nitro-N-nitrosoguanidine alone. The incidence of adenocarcinoma in the glandular stomach also was high only in the 4th-wk group of gastrin-treated rats. However, these effects could not be seen in other gastrin-treated or untreated groups of rats. The data suggest that gastrin treatment in the early stage of rat stomach carcinogenesis by N-methyl-N'-nitro-N-nitrosoguanidine is effective in increasing the development of gastric tumors. (Author abstract) (21 Refs)

OTHER STUDIES OF THE MODIFICATION OF CARCINOGENESIS

12. EFFECTS OF DELAYS IN THE CELL CYCLE ON THE INDUCTION OF PRENEOPLASTIC AND NEOPLASTIC LESIONS IN RAT LIVER BY 1,2-DIMETHYLHYDRAZINE.

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Dept. Pathology, Univ. Toronto, Toronto, Ontario M5G 1L5, Canada
Cancer Res; 42(3):876-880 1982

This study was designed to explore further the relationship between cell proliferation and the induction of early putative preneoplastic lesions by carcinogens. Rats were given a non-necrogenic dose of 1,2-dimethylhydrazine 24 hr before being subjected to partial hepatectomy. Beginning 4 hr later, hydrocortisone was injected 10x at 4-hr intervals to delay progression through the cell cycle, including inhibition of DNA synthesis by at least 85% for about 40 hr. At the appropriate time thereafter, the putative preneoplastic hepatocytes were selectively stimulated to grow in vivo into gamma-glutamyltransferase-positive focal lesions. Animals given hydrocortisone showed a large decrease (71%) in the number of gamma-glutamyltransferase-positive foci. In contrast, when hydrocortisone was given at 6 days after partial hepatectomy, no inhibition in the induction of hepatic lesions was observed. In the next experiments, rats were treated with 1,2-dimethylhydrazine and were subjected to partial hepatectomy at 12, 24, or 84 hr or 1 wk thereafter. A significant number of gamma-glutamyltransferase-positive foci was found when partial hepatectomy was performed at 12 or 24 hr but far fewer were found when the operative partial hepatectomy was delayed to 48 hr or 1 wk later. Similarly, in long-term experiments, 6 of 14 animals developed primary hepatocellular carcinoma 13 mo after the time of injection of 1,2-dimethylhydraz ine when partial hepatectomy was performed at 12 hr, while none of the animals developed liver cancer when the operation was performed at 48 hr. These results imply that the majority of biochemical lesions induced by 1,2-dimethylhydrazine that are relevant to the induction of liver preneoplasia and neoplasia are short-lived and that their persistence is associated with some cellular activity closely related to the cell cycle. (Author abstract) (39 Refs)

13. INDUCTION OF GAMMAGLUTAMYLTRANSPEPTIDASE-POSITIVE ALTERED HEPATOCYTIC LESIONS BY COMBINATION OF TRANSPLACENTAL-INITIATION AND POSTNATAL-SELECTION.

Ogawa K, Yokokawa K, Tomoyori T, Onoe T
Dept. Pathology, Sapporo Medical Coll., Sapporo 060, Japan
Int J Cancer; 29(3):333-336 1982

The purpose of this study was to induce in postnatal life the selective growth of altered hepatocytic populations which had been induced in utero by various chemicals. Pregnant rats of a Wistar strain were given a single dose of various chemical carcinogens on the 18th gestational day. From 2 mo postpartum, both the mothers and offspring were given a diet containing 2-acetylaminofluorene (2-AAF) at a concentration of 0.02% for 2 wk. Then, at the end of the 1st wk after the 2-AAF feeding, a two-thirds partial hepatectomy was performed. All the animals were killed 1 wk after the partial hepatectomy and were examined for the incidence of gamma-glutamyltranspeptidase (GGT)-positive altered hepatocytic foci in the liver. The transplacental administration of not only a hepatic carcinogen, diethylnitrosamine (DEN) but also 7,12-dimethylbenzanthracene (DMBA), which does not usually produce hepatocellular carcinomas in adult rats, induced GGT-positive altered hepatocytes in the liver of the offspring. These hepatocytes grew into grossly visible hyperplastic nodules within a wk after the two-thirds partial hepatectomy. The possible applicability of the transplacental initiation-postnatal selection model for the short-term assay of transplacental carcinogenicity is discussed. (Author abstract) (21 Refs)

14. EFFECTS OF AGING ON THE INDUCTION OF ANGIOSARCOMA.

Groth DH, Coate WB, Ulland BM, Hornung RW
Div. Biomedical and Behavioral Science, Natl. Inst. Occupational Safety and Health
Environ Health Perspect; 41:53-57 1981

The effects of aging on chemical induction of angiosarcoma were studied in adult Sprague-Dawley albino rats. In each of four age groups (6, 18, 32, and 52 wk old at the start of exposure), 110-128 male rats and an equal number of female rats were exposed to vinyl chloride (VC: 948 ppm, 7 hr/day, 5 days/wk for a mean duration of 24.5 wk). Equal numbers of controls were kept under identical conditions but were not exposed to VC. Rats exposed to VC did not show any significant differences in mean hematological or clinical chemistry measurements at interim sacrifice times when compared with controls. Angiosarcomas were found in 28/370 exposed males and 50/387 exposed females; among controls only one sc angiosarcoma was found. Angiosarcomas occurred more frequently with increasing age at the start of exposure. Among male rats killed at unscheduled times, the occurrence rates were 0% for 6-wk-, 0% for 17-wk-, 6.7% for 32-wk-, and 24% for 52-wk-old rats. The corresponding rates for female rats were 5.3%, 15%, 47%, and 20%. Times between start of exposure and first appearance of tumors were shorter in older rats than in younger rats. Most of the angiosarcomas in exposed rat were highly anaplastic primary tumors of the liver with pulmonary metastases. Results indicate that older rats and female rats are more susceptible to induction of angiosarcomas by VC than younger rats and female rats, respectively. (3 Refs)

15. EFFECT OF AGING ON THE DEVELOPMENT OF 1,2-DIMETHYLHYDRAZINE-INDUCED INTESTINAL TUMORS IN MICE.

Turusov VS, Lanko NS, Parfenov IuD
Lab. Carcinogenic Agents, All-Union Cancer Res. Center, Moscow, USSR
Biull Eksp Biol Med; 91(12):705-707 1981

Relationship between carcinogenesis and aging was studied in young (2 mo old), mature (8 mo old), and old (12 mo old) female CBA mice. Animals received sc injections of 1,2-dimethylhydrazine (DMH: 8 mg/kg, 1x/wk). Animals were followed up for 26-35 wk after the initiation of DMH administration, and the incidence of tumors of the large intestine was determined. An overall incidence of tumors in young, mature, and old mice was 13.1%, 61.0%, and 69.1%, respectively. The frequency of infiltrating tumors was 6%, 30.5%, nad 54.3%, respectively. Analysis of time-effect curves showed that the median latent period of tumor development in young mice was approx 1.8x greater than that in old mice and 1.4x greater than that in mature mice. The differences in the chemical carcinogenesis were explained by elevated activity of beta-glucuronidase in the large intestine of old mice. (7 Refs) (In RUS)

STUDIES OF TUMOR PROMOTION OR COCARCINOGENESIS IN MOUSE SKIN

16. HISTOLOGICAL, PROLIFERATIVE, AND BIOCHEMICAL ALTERATIONS IN DORSAL EPIDERMIS OF THE SYRIAN GOLDEN HAMSTER INDUCED BY 12-O-TETRADECANOYLPHORBOL-13-ACETATE AND THE CALCIUM IONOPHORE A 23187.

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Cancer Res; 42(5):2034-2039 1982

Long-term treatment with 12-O-tetradecanoylphorbol-13-acetate (TPA) of dorsal skin of 7,12-dimethylbenz(a)anthracene-initiated Syrian golden hamsters does not lead to the formation of epithelial tumors and leaves the epidermis essentially unchanged. However, previous histological studies by others have shown that hamster epidermis can be hyperplastically transformed by a single app lication of TPA but that the tissue is capable of gradually adapting to the drug after extended TPA exposure. We have investigated the response of hamster back epidermis to single and multiple treatments with increasing doses of TPA with regard to histological, proliferative, and biochemical alterations, and we show that in our animal strain the dorsal epidermis is resistant to even a single exposure to TPA, although the clearance rate of TPA is comparable to that in mouse epidermis and the metabolism of the substance is negligible. In contrast, the epidermis could be moderately stimulated by a single application of the nonpromoting calcium ionophore A 23187 and exhibited a strong proliferate and hyperplastic response following the simultaneous exposure to the calcium ionophore and TPA. Both types of hyperproliferation did not reveal an initial depression of the proliferative activity and were accompanied by typical alterations of the keratin polypeptide pattern, which was not detectable after treatment with TPA alone. (Author abstract) (21 Refs)

17. EFFECT OF THE ACTIVE TUMOR PROMOTER, 12-O-TETRADECANOYLPHORBOL-13-ACETATE ON HAIR FOLLICULAR GROWTH AND DEVELOPMENT OF HAIR ANLAGE TUMORS IN THE MOUSE SKIN: A COMPARISON WITH HUMAN ADNEXAL LESIONS.

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Ultrastructure Div., Cancer Res. Inst., Parel, Bombay 400012, India
J Cancer Res Clin Oncol; 102(3):245 252 1982

Effect of the active tumor promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA), on the induction of hair follicular growth and possible neoplasia was studied histologically in normal and precancerous mouse skin. Biweekly application of TPA resulted in nevoid proliferation of hair follicles, decreased the latent period of tumor induction, and increased the number of carcinomas of hair follicular origin in mice pretreated with MCA. The experimental tumor induction data was compared with human adnexal tumors of hair follicular origin. Similar types of animal and human lesions could be attributed to the promoter effect alone or to the dual influence of a carcinogen and promoter. (Author abstract) (11 Refs)

18. SYSTEMIC INFLUENCE OF PRE-IRRADIATION OF A LIMITED SKIN AREA ON UV-TUMORIGENESIS.

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Photochem Photobiol; 35(3):379-383 1982

It has been established that chronic UV irradiation of mice produces a systemic effect. The animals become incapable of rejecting an implanted UV-induced tumor. A possible consequence of the induction of this systemic effect could be an enhancement of the de novo formation of tumors by chronic UV irradiation. We have therefore carried out an investigation to determine whether such an effect is demonstrable in an animal model. Hairless mice (Skh hr 1) were pre-irradiated for a few mo with UV radiati on while certain skin areas of the animals were shielded from the radiation. Subsequently, the initially shielded skin areas were chronically exposed to UV radiation, which resulted in the development of tumors in these skin areas. It was found that the formation of tumors in the initially shielded skin areas was enhanced by the pre-irradiation of the other skin areas. Thus, a systemic effect appeared to have influenced the development of tumors in the initially shielded skin areas. (Author abstract) (12 Refs)

19. DIFFERENT EFFECTS OF DIMETHYLBENZ(A)ANTHRACENE AND TETRADECANOYLPHORBOL ACETATE ON DIFFERENTIATION OF MAST CELLS IN THE SKIN OF MICE.

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Am J Pathol; 106(3):312-317 1982

The effects of the application of 7,12-dimethylbenz(a)anthracene (DMBA) and 12-O-tetradecanoylphorbol-13-acetate (TPA) on the differentiation of tissue mast cells were investigated. Giant granules of beige (C57BL/6-bgJ/bgJ, Chediak-Higashi syndrome) mice were used to distinguish different populations of mast cells. In the normal C57BL/6 mice that had been irradiated and injected with bone marrow cells of beige C57BL/6 mice (bgJ/bgJ to +/+ chimeras), mast cells in the skin remained normal in type and mast-cell precursors in the bone marrow and peripheral blood were of the beige type. When DMBA was painted onto the skin of such bgJ/bgJ to +/+ chimeras, the number of beige mast cells increased, but the number of normal mast cells did not change. On the other hand, the number of both normal and beige mast cells increased when TPA was applied to the bgJ/bgJ to +/+ chimeras. Autoradiographic study showed that beige mast cells proliferated more than normal mast cells after DMBA applications, whereas the proliferation was comparable in both types of mast cells after TPA applications. The present results indicate that the effects of DMBA applications on differentiation of mast cells are different from those of TPA applications. (Author abstract) (18 Refs)

20. EFFECT OF VITAMIN B2 ON TUMORIGENESIS OF 3-METHYLCHOLANTHRENE IN THE MOUSE SKIN.

Ohkoshi M, Ohta H, Ito M
Dept. Oral Surgery, Nagoya Univ. Sch. Medicine, 65, Tsurumai-cho, Showa-ku, Nagoya 466, Japan
Gan; 73(1):105-107 1982

Local administration of riboflavin 2',3',4',5'-tetrabutyrate (B2-But4) suppressed the induction of skin tumors in mice by

3-methylcholanthrene. The latent period for the appearance of tumors was markedly delayed in the group treated with B2-But4. These findings suggest that riboflavin might retard the process of skin tumorigenesis. (Author abstract) (11 Refs)

21. RETINOIC ACID MODULATION OF ULTRAVIOLET LIGHT-INDUCED EPIDERMAL ORNITHINE DECARBOXYLASE ACTIVITY.

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J Invest Dermatol; 78(2):121-124 1982

Irradiation of skin with UV light of sunburn range (UVB) leads to a large and rapid induction of the polyamine biosynthetic enzyme ornithine decarboxylase in the epidermis. Induction of epidermal ornithine decarboxylase also occurs following application of the tumor promoting agent 12-O-tetradecanoylphorbol-13 acetate and topical retinoic acid is able to block both this ornithine decarboxylase induction and skin tumor promotion. In the studies described below, topical application of retinoic acid to hairless mouse skin leads to a significant inhibition of UVB-induced epidermal ornithine decarboxylase activity. The degree of this inhibition was dependent on the dose, timing, and frequency of the application of retinoic acid. To show significant inhibition of UVB-induced ornithine decarboxylase the retinoic acid had to be applied within 5 hr of UVB irradiation. If retinoic acid treatment was delayed beyond 7 hr following UVB, then no inhibition of UVB-induced ornithine decarboxylase was observed. The quantities of retinoic acid used (1.7 nmol and 3.4 nmol) have been shown effective in inhibiting 12-O-tetradecanoyl phorbol-13 acetate induced ornithine decarboxylase. The results show that these concentrations of topical retinoic acid applied either before or immediately following UVB irradiation reduces the UVB induction of epidermal ornithine decarboxylase. The effect of retinoic acid in these regimens on UVB-induced skin carcinogenesis is currently under study. (Author abstract) (20 Refs)

CELL CULTURE STUDIES OF MECHANISMS OF MODIFICATION

22. IDENTIFICATION OF ASCORBIC ACID AS THE HEAT-STABLE FACTOR FROM BRAIN WHICH INACTIVATES THE PHORBOL ESTER RECEPTOR.

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Cancer Res; 42(4):1227-1232 1982

Homogenates of calf cortex contained a heat-stable, low-molecular-weight factor which inhibited in a dose-dependent, irreversible, and noncompetitive manner the binding of [20-3H]phorbol-12,13-dibutyrate to its receptor in brain particulate preparations. The inhibitory factor was identified as ascorbic acid. As in other cases in which ascorbic acid alters the activity of membrane proteins, inactivation of phorbol ester binding by ascorbic acid was not stereospecific, correlated with stimulation of lipid peroxidation, and could be blocked by inhibitors of lipid peroxidation. Free radical-mediated receptor inactivation could potentially play a role in systems in which phorbol esters stimulate the generation of active oxygen species or fatty acid hydroperoxides. In addition, protection of the [20-3H]phorbol-12,13-dibutyrate receptor from free radical damage would be desirable in the screening of extracts for competitive inhibitory activities. (Author abstract) (54 Refs)

23. RESOLUTION OF HIGH AND LOW AFFINITY EPIDERMAL GROWTH FACTOR RECEPTORS. INHIBITION OF HIGH AFFINITY COMPONENT BY LOW TEMPERATURE, CYCLOHEXIMIDE, AND PHORBOL ESTERS.

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Dept. Molecular Biology, Wellcome Res. Lab., Research Triangle Park, NC, 27709
J Biol Chem; 257(6):3053-3060 1982

Receptors for the mitogen epidermal growth factor (EGF) have been implicated as mediators of cellular transformation and tumor promotion. 12-O-Tetradecanoylphorbol-13-myristate (PMA) causes immediate but transient reductions in the ability of human KB cells to internalize EGF by decreasing the affinity of cell surface EGF receptors 7-to 12-fold. After 90 min of PMA exposure, complete recovery of the high affinity apparatus occurs. Evidence is presented that the decreased binding capacity to 125I-EGF is caused by delaying the appearance at the plasma membrane of cryptic receptor sites of high affinity. Exposure of these high affinity binding sites is temperature dependent and is blocked by pretreatment of cells with inhibitors of de novo protein synthesis. After short incubation periods (0 to 60 min) with 125I-EGF, up to 90% of the internalized 125I-EGF can be rapidly dissociated from cells by the addition of PMA. This treatment kinetically reveals a trypsin-insensitive, nondissociating component of cell-associated 125I-EGF. With PMA, both the rate (maximal at 4 hr with PMA as compared to 24 hr) and extent (8-fold greater with PMA) of transfer of 125I-EGF into this trypsin-stable compartment is enhanced and accounts for the severalfold stimulation in 125I-EGF accumulation. This evidence suggests that the internalization of 125I-EGF can be resolved into two components, one into which EGF immediately partitions and is freely exchangeable with the extracellular medium and that is disrupted by PMA. A second and previously unknown compartment retains 125I-EGF in the presence of PMA after a short delay to a considerably greater extent than that of untreated cells. Thus, without PMA, EGF is internalized into this nondissociating intracellular compartment, but the transfer is only 5-10% as efficient. These results suggest that the accumulation of stable intracellular mitogen-receptor complexes may be directed by a population of very high affinity receptors which may be an element involved in the control of cellular growth and tumor promotion. (Author abstract) (46 Refs)

24. EFFECTS OF PHORBOL ESTERS ON BASAL EPIDERMAL CELLS DERIVED FROM EAR SKIN OF ADULT GUINEA PIGS.

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Cancer Res; 42(5):1975-1979 1982

In cultures of basal epidermal cells obtained from ear skin of adult guinea pigs , the tumor-promoting phorbol ester 12-O-tetradecanoylphorbol-13-acetate induces cellular proliferation which is prostaglandin dependent and inhibited by indomethacin. Inhibition by indomethacin can be overcome by prostaglandins E2 and F2alpha, with prostaglandin F2alpha being more effective. The concomitant induction of ornithine decarboxylase activity is insensitive to indomethacin inhibition. The nonpromoting derivative 4-O-methyl-12-O-

tetradecanoylphorbol-13-acetate evokes a prostaglandin-independent, ie, indomethacin-insensitive, stimulation of cell proliferation without inducing ornithine decarboxylase activity. (Author abstract) (28 Refs)

25. EFFECTS OF TUMOR-PROMOTING PHORBOL DIESTERS ON NEOPLASTIC PROGRESSION OF SYRIAN HAMSTER EMBRYO CELLS.

O'Brien TG, Saladik D, Diamond L
Wistar Inst. Anatomy and Biology, Philadelphia, PA, 19104
Cancer Res; 42(4):1233-1238 1982

The progression of normal Syrian hamster embryo cells to a neoplastic phenotype after treatment with a chemical carcinogen and continuous exposure to phorbol ester tumor promoters was studied in cell culture. Tumor promoters were able to rescue cell lines derived from individual carcinogen-treated colonies from a program of cellular senescence. In general, these cell lines did not grow in soft-agar medium or produce tumors in newborn hamsters at early passages but acquired these properties at later passages. These cell lines were used to study the temporal acquisition of a phenotypic characteristic of neoplastic rather than normal hamster embryo cells: the synergistic induction of the enzyme ornithine decarboxylase (ODC) by tumor promoter and serum growth factors. All cell lines that acquired neoplastic status with passage in culture exhibited the synergistic induction of ODC prior to their acquisition of the ability to either grow in soft-agar medium or produce tumors in newborn hamsters. Cell lines that responded to promoters with the synergistic induction of ODC accumulated greater levels of polyamines, especially putrescine, after promoter treatment than did normal cells. Tumor promoters did not affect the percentage of cells labeled with [3H]thymidine in preneoplastic cell lines, a finding similar to previous results in normal and neoplastic hamster cells. These studies demonstrate that tumor promoters can affect the early stages of neoplastic progression in carcinogen-treated Syrian hamster embryo cells and that a particular phenotypic property found in neoplastic hamster cells, the synergistic induction of ODC by tumor promoters and serum growth factors, is acquired by cell lines before they acquire neoplastic potential. (Author abstract) (25 Refs)

26. 12-O-TETRADECANOYLPHORBOL-13-ACETATE (TPA) INDUCES SISTER-CHROMATID EXCHANGES AND DELAYS IN CELL PROGRESSION IN CHINESE HAMSTER OVARY AND HUMAN CELL LINES.

Schwartz JL, Banda MJ, Wolff S
Lab. Radiobiology, Univ. California, San Francisco, CA, 94143
Mutat Res; 92(1/2):393-409 1982

In Chinese hamster ovary (CHO) cells and SV40-transformed human fibroblast cell lines (GM637 and XP12RO), 12-O-tetradecanoylphorbol-13-acetate (TPA: 1.0 nanog-1.0 ug/ml) caused a 20-45% increase in the frequency of sister chromatid exchanges (SCEs). This increase in SCEs was not caused by an impurity in the TPA preparation, or increased 5-bromo-2'-deoxyuridine uptake into DNA; it was independent of the incubation time between TPA exposure and fixation of the cells. Simultaneous exposure to TPA (1.0 ug/ml) and benzo(a)pyrene (BP: 1.7 x 10(-5)-3.3 x 10(-6) M) led to a synergistic SCE induction in CHO cells. No synergism was observed after simultaneous exposure to TPA (1 ug/ml) and mitomycin C (0.03 ug/ml) or UV light. In addition to its weak SCE-inducing effects in CHO cells, TPA alone caused a slight delay in cell cycle progression and markedly enhanced the cell cycle delay induced by BP. The SCE-inducing capacity of TPA in these cells was unrelated to its toxicity, because TPA was not toxic at the doses used. It also seemed to be unrelated to excision repair capacity, because TPA caused similar increases in SCE frequency in cells which were proficient (GM637), mildly deficient (CHO), and severely deficient (XP12RO) in excision repair. The significance of SCE induction and its relationship to other biologic effects of TPA remain unknown. (40 Refs)

27. 12-O-TETRADECANOYL-PHORBOL-13-ACETATE AND ITS RELATIONSHIP TO SCE INDUCTION IN SYRIAN AND CHINESE HAMSTER CELLS.

Popescu NC, Amsbaugh SC, Larramendy ML, DiPaolo JA
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Environ Mutagen; 4(1):73-81 1982

Alteration of cell culture conditions, 12-O-tetradecanoylphorbol-13-acetate (TPA), or 5-bromodeoxyuridine (Burd) concentrations, or temporal relation between UV or x-irradiation and TPA had no effect on sister chromatid exchange (SCE) induction of Syrian hamster embryo cells (HEC). SCE frequencies were determined on exponentially growing and stationary HEC cultures incubated with different Burd concentrations for one or two replicative cycles. TPA (0.01-2.0 ug/ml medium) was ineffective in inducing SCE in HEC cultures cultivated in medium supplemented with heat-inactivated serum, independent of Burd concentration (1.0-10.0 ug/ml) and the number of cell divisions post treatment. In a similar study, TPA did not increase SCE frequency in V79-4 Chinese hamster cells in heat-inactivated or noninactivated serum. TPA has no effect on UV or x-irradiation induced SCE. X-irradiation (200 R) causes an increase of only 1 SCE/cell over the control value, while UV (1.5 and 3.0 J/square meter) causes an increase of 10 and 24 SCE per metaphase. TPA addition either immediately or 48 hr after UV or x-irradiation did not alter SCE frequency obtained by irradiation alone. Although SCE induction may be important for the induction of transformation by environmental agents, the enhancement of transformation frequency caused by TPA occurs without further DNA alterations involved in SCE formation. (21 Refs)

28. CA-CALMODULIN MEDIATES THE DNA-SYNTHETIC RESPONSE OF CALCIUM-DEPRIVED LIVER CELLS TO THE TUMOR PROMOTER TPA.

Jones A, Boynton AL, Macmanus JP, Whitfield JF
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Exp Cell Res; 138(1):87-93 1982

Incubation in low (0.02 mM)-calcium medium inhibited the proliferation of T51B rat liver cells. Addition of TPA (12-O-tetradecanoyl-phorbol-13-acetate; 50 ng/ml) or calcium (1.25 mM) caused the arrested, calcium-deprived cells to initiate DNA synthesis within 2 hr and eventually to resume proliferating. The rapid DNA-synthetic response to TPA addition appeared to depend on the small amount of calcium remaining in the calcium-deficient medium, because it was blocked by correspondingly small amounts of the specific calcium chelator EGTA or La+++, which displaces calcium from the cell surface and inhibits transmembrane calcium fluxes. The common mediation of TPA and calcium actions through Ca-calmodulin complexes was indicated by the following observations: The DNA-synthetic responses to both agents were blocked by the supposedly specific Ca-calmodulin blocker trifluoperazine; the trifluoperazine-induced block was overcome by pure calmodulin; and the responses to both TPA and cal-

cium were blocked by anti-calmodulin antibodies. (Author abstract) (35 Refs)

29. RETINOIC ACID INDUCES ANCHORAGE- AND DENSITY-DEPENDENT GROWTH WITHOUT RESTORING NORMAL CYTOSKELETON, EGF BINDING, FIBRONECTIN CONTENT AND ODC ACTIVITY IN A RETROVIRUS-TRANSFORMED MOUSE CELL LINE.

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Exp Cell Res; 138(1):95-107 1982

We studied the effects of retinoic acid (RA), a known tumor inhibitor, on a group of transformation-related properties expressed by a Kirsten sarcoma virus (Ki-MSV)-transformed BALB/c 3T3 (clone A31) cell line (KA31). The aim was to determine whether any one or a group of such transformation-specific changes, exhibited by this cell line, is an absolute prerequisite for its acquisition of the neoplastic state. Our study shows that RA treatment restores two important parameters of normalcy in KA31 cells: density-dependent growth inhibition, and anchorage-dependent growth. Retinoic acid also induces cell-to-substratum adhesiveness in a significant proportion of the treated KA31 cell population. However, four other markers of transformation - loss of microfilaments, lack of surface fibronectin, reduced epidermal growth factor (EGF) binding, and increased ornithine decarboxylase activity - remain unaltered by RA treatment. These transformation-specific changes, therefore, are dissociable from loss of anchorage- and density-dependent growth. It is suggested that RA may intervene in transforming protein kinase-induced cell surface changes that are involved in cellular malignancy and the loss of growth control in KA31 cells. (Author abstract) (57 Refs)

30. STIMULATION OF DNA SYNTHESIS IN MURINE FIBROBLASTS BY THE TUMOUR PROMOTER TELEOCIDIN: RELATIONSHIP TO PHORBOL ESTERS AND VASOPRESSIN.

Collins M, Rozengurt E
Imperial Cancer Res. Fund Laboratories, Lincoln's Inn Fields, London WC2A 3PX, England
Biochem Biophys Res Commun; 104(4):1159-1166 1982

The influence of the tumor promoter teleocidin (TL) on initiation of DNA synthesis was studied in quiescent Swiss 3T3 and other cells. As determined with the use of (3H)thymidine, TL at 20 nanoM (nM) markedly enhanced DNA synthesis at suboptimal concentrations of serum in Swiss 3T3 cells. In the presence of 2.5% serum, which does not support growth of the 3T3 cells, TL (100 nM) stimulates confluent cells to form multiple layers after 4 days incubation. In serum-free medium, 20 nM TL stimulated DNA synthesis when added in combination with retinoic acid, epidermal growth factor, cholera toxin, platelet-derived growth factor, insulin, fibroblast-derived growth factor (FDGF), and phorbol-12,13-dibutyrate (PDBu). Synergism was shown with FDGF when both TL and retinoic acid were present. No synergism between PDBu and TL was shown in any of the cell types used. Several lines of evidence indicate that TL and phorbol esters bind to the same receptor, or their actions could converge at a post-receptor locus. Thus, prolonged treatment of Swiss 3T3 cells with PDBu leads to a marked decrease in (3H)-PDBu binding sites and marked reduction in subsequent mitogenic response not only to phorbol esters, but also to TL. TL is not synergistic with vasopressin, suggesting that it utilizes the same mitogenic pathway as this physiological ligand. (17 Refs)

31. A NEW INTERCELLULAR COMMUNICATION ASSAY: ITS USE IN STUDIES ON THE MECHANISM OF TUMOUR PROMOTION.

Fitzgerald DJ, Murray AW
Sch. Biological Sciences, Flinders Univ., Bedford Park, 5042, South Australia
Cell Biol Int Rep; 6(3):235-242 1982

A rapid, quantifiable technique capable of measuring the transfer of nucleotides between cells over periods as short as 30 min is reported. The method was used to extend previous work showing inhibition of intercellular communication by tumor-promoting phorbol esters. When cocultures of mouse epidermal cells (HEL-37) and mutant mouse fibroblast cells (PG-19) were incubated in 3 milliM ED TA, essentially all PG-19 cells and approx 20% of the HEL-37 cells were released, whereas cultures of HEL-37 cells alone released only about 2% of the cells. The extra HEL-37 cells released in coculture were probably those in contact with PG-19 cells, and were presumably involved as donor cells for the junctional transfer of labeled nucleotides. Results of a 3-hr autoradiographic analysis using 3H-hypoxanthine indicated that approx 33% of the released PG-19 cells were labeled by such transfer. Further results indicated that the av incorporation of 3H-thymidine and 14C-hypoxanthine per HEL-37 cell was the same in cells released from cocultures by EDTA treatment and those maintained in culture alone. Thus, alteration in the 3H:14C ratio in the released cells provides a direct measure of the transfer of labeled nucleotides from HEL-37 donor cells to PG-19 recipient cells, presumably via gap junctions. After a short lag period, continuous transfer of radioactivity to the PG-19 cells occurred for at least 3 hr. Transfer was inhibited by 12-O-tetradecanoylphorbol 13-acetate. (9 Refs)

32. TUMOR PROMOTER STIMULATION OF PHOSPHATIDYLCHOLINE TURNOVER IN HELA CELLS.

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Cancer Res; 42(5):1980-1985 1982

Incubation of HeLa cells for 24 hr with [3H]choline resulted in extensive labeling of the phosphorylcholine and phosphatidylcholine pools. 12-O-Tetradecanoylphorbol-13-acetate (TPA), other phorbol ester tumor promoters, and mezerein stimulated the release of [3H]choline and [3H]phosphorylcholine from such prelabeled cells. The release was accompanied by decreased radioactivity in the phosphorylcholine pool, raising the possibility that the released materials were derived by leakage from this pool. However, TPA did not induce the release of radioactivity from cells containing a prelabeled nucleotide pool. Similarly, the TPA-stimulated release of radioactivity for prelabeled cells closely paralleled the label present in the phospholipid pool rather than the phosphocholine pool. Consequently, it is suggested that the primary source of the released material is phosphatidylcholine acting as a substrate for a phospholipase C enzyme. TPA also stimulated the incorporation of [3H]choline into phospholipids, but a time-course study indicated that that phospholipase C activation preceded this event. This was supported by the observation that incorporation of [3H]choline was also stimulated by exogenously added phospholipase C. (Author abstract) (29 Refs)

33. TUMOR PROMOTER-STIMULATED SYNTHESIS OF MASON-PFIZER MONKEY VIRUS.

Wunderlich V, Baumbach L, Sydow G
Central Inst. Cancer Res., Acad. Sciences German Democratic Republic, Lindenberger Weg 70/80, DDR-1115 Berlin, E. Germany
J Cancer Res Clin Oncol; 102(3):271-275 1982

The tumor promoter 12-O-tetradecanoyl-phorbol-13-acetate (TPA) increases by severalfold the synthesis of Mason-Pfizer monkey virus (MPMV), a type D retrovirus, when the virus is growing in human embryo kidney (HEK) cells. The effect is transient and paralleled by a striking morphological alteration of the cells. The optimal TPA concentration for stimulation is 5 ng/ml. Contrary to infected HEK cells, TPA induces at similar concentrations neither stimulation of MPMV synthesis nor altered morphology in persistently MPMV-infected cells of the continuous human tumor cell line A 204. (Author abstract) (15 Refs)

34. IDENTIFICATION OF PHORBOL ESTER RECEPTORS IN T-CELL GROWTH FACTOR-PRODUCING AND - NONPRODUCING EL4 MOUSE THYMOMA CELLS.

Sando JJ, Hilfiker ML, Piacentini MJ, Laufer TM
Dept. Pharmacology, Univ. Virginia Sch. Medicine, Charlottesville, VA, 22908
Cancer Res; 42(5):1676-1680 1982

Two lines of EL4 mouse thymoma cells have been examined for the presence of specific phorbol ester-binding components. Both lines displayed saturable specific binding as determined by using [20-3H]phorbol 12,13-dibutyrate in a whole-cell-binding assay. Specific binding in each line was max within 10 min at 37 C but rapidly decreased to about 30% within 30 min. Max binding at 4 C was reached after 60 min and was stable for at least 8 hr; however, this level was only about 30% of the max obtained at 37 C. Saturation of the specific binding after 3 hr at 4 C occurred at a concentration (30 to 50 nM) which is consistent with that yielding max T-cell growth factor production in the responding line but greater than that at which inhibition of proliferation was detected in those cells. Scatchard analysis of these data was consistent with the existence of a single class of binding sites with a Kd of 11 +-0.6 (SD) nM for the T-cell growth factor-producing cells and 18 +-1.9 nM for the nonproducing line. The numbers of sites per cell measured in the responding and nonresponding lines were 5.6 +-1.3 x 10(4) and 7.1 +-0.2 x 10(4), respectively. Competition by a series of phorbol esters for [20-73 1H]phorbol 12,13-dibutyrate binding in the responding line showed the same order of potency as production of T-cell growth factor and inhibition of proliferation by the analogs. These data support identification of the phorbol ester-binding component in the responding cells as the receptor mediating T-cell growth factor production. The presence of binding components in unresponsive cells in numbers and with characteristics indistinguishable from those of responsive cells suggests that the failure to respond is due to modification of a step which succeeds the initial binding event. (29 Refs)

35. PREVENTION OF INTERFERON-INDUCED AUGMENTATION OF CELLULAR ANTITUMOR EFFECTOR MECHANISMS BY PHORBOL ESTERS.

Keller R, Aguet M, Tovey M, Stitz L
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Cancer Res; 42(4):1468-1472 1982

Both natural killer cell- and macrophage-mediated spontaneous in vitro cytotoxicity for tumor targets is rapidly and strongly augmented by interferon. Macrophage-activating lymphokines considerably enhance macrophage-tumoricidal activity but did not affect natural killer cell-type cytotoxicity. Augmentation of cytolytic capacity by interferon and by macrophage-activating lymphokines is prevented by the tumor-promoting phorbol ester, 12-O-tetradecanoylphorbol-13-acetate. However, the classical antiviral activity and the specific binding of interferon to cell surface receptors remains unaffected by 12-O-tetradecanoylphorbol-13-acetate. (Author abstract) (27 Refs)

36. MODULATION OF NATURAL KILLER SENSITIVITY OF MURINE TROPHOBLAST CELLS BY TUMOR PROMOTER AND INTERFERON.

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Lab. Cell Biology, NCI, Bethesda, MD, 20205
Int J Cancer; 29(3):315-321 1982

The in vitro established lines of murine placental trophoblast cells showed little membrane expression of H-2 antigens and a high degree of sensitivity to natural killer (NK)-cell-mediated cytotoxicity. This NK-sensitivity was decreased either by short-term treatment of these cells with murine interferon (IFN) or by culture for more than 4 days in the presence of a tumor promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA). This effect of TPA was reversible after removal of TPA from the culture medium. However, IFN treatment of trophoblast cells cultured previously in TPA medium resulted in restoration of NK-sensitivity to the original level exhibited by cells untreated with IFN or TPA. The mechanism for this antagonistic effect is not clear. The decrease in NK-sensitivity of IFN- or TPA-treated trophoblast cells was not due to the loss of NK-recognition membrane structures, or to induction of prostaglandin which elevates cyclic-AMP levels. Inhibition of protein synthesis by cycloheximide restored the NK-sensitivity of TPA-treated trophoblast cells, indicating the possible contribution of de novo synthesized protein(s) which could confer NK-resistance. The TPA-treated trophoblast cells became more tumorigenic, producing larger tumors and a higher mortality than the untreated controls when inoculated into mice. The possible roles of NK cells in trophoblastic diseases and feto-maternal relationships are discussed. (Author abstract) (27 Refs)

37. ACTIVATION OF MONOCYTE AND GRANULOCYTE ANTIBODY-DEPENDENT CYTOTOXICITY BY PHORBOL MYRISTATE ACETATE.

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Div. Hematology/Oncology, Ohio State Univ. Hosp., Columbus, OH, 43210
Infect Immun; 35(3):818-825 1982

We have characterized the effects of phorbol myristate acetate (PMA) on human mo nocyte and neutrophil oxidative metabolism and antibody-dependent cytotoxicity toward anti-D sensitized human erythrocytes (RBC) and a human lymphoblastoid cell line (CEM). Hexose monophosphate shunt activity was measured by [1-14C]glucose oxidation and target lysis by 51Cr release. PMA produced a dose-dependent stimulation of hexose monophosphate shunt activity. Neutrophils responded with higher hexose monophosphate shunt activity and at a lower PMA concentration than did monocytes. PMA increased monocyte lysis of antibody-sensitized RBC by two-thirds, but did not affect lysis of CEM targets. Neutrophils were unable to lyse either antibody-sensitized or nonsensitized RBC without the addition of PMA. When PMA was added, lysis of both tar-

gets increased markedly. Neutrophils without PMA were able to lyse a small number of both antibody-sensitized and nonsensitized CEM targets. PMA also increased neutrophil lysis of these targets. Target lysis by neutrophils from a patient with chronic granulomatous disease, cells unable to produce reactive oxygen species, was not increased by PMA. Chronic granulomatous disease monocytes, however, responded to PMA by more than doubling lysis of antibody-sensitized RBC. Hypoxia inhibited PMA augmentation of antibody-sensitized RBC lysis by neutrophils, but not by monocytes. Generation of reactive oxygen species by the xanthine-xanthine oxidase system inhibited CEM growth, but did not cause lysis, indicating that in some cases oxidative injury may be nonlytic. We suggest that PMA augments neutrophil cytotoxicity to tumor and RBC targets by stimulating reactive oxygen species-mediated lysis, but in monocytes augmentation of lysis is due to activation of a nonoxidative mechanism of lysis. (Author abstract) (43 Refs)

38. EFFECTS OF A TUMOR PROMOTER, 12-O-TETRADECANOYL-PHORBOL-13-ACETATE (TPA) ON HUMAN PERIPHERAL BLOOD LYMPHOCYTES: INDUCTION OF SUPPRESSOR T CELLS AND REDUCTION OF NATURAL KILLING (NK) AND ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY (ADCC).

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Dept. Obstetrics and Gynecology, Mie Univ. Sch. Medicine, Tsu, Japan
Mie Med J; 31(1):37-52 1981

Effects of the tumor promoter, 12-O-tetradecanoyl-phorbol-13-acetate (TPA) were studied in human peripheral blood lymphocytes (PBL) from normal healthy adult donors. Cell suspensions of T cells, B cells, and monocytes were exposed to TPA, concanavalin A (ConA), phytohemagglutinin (PHAP), and pokeweed mitogen (PWM) in various combinations and concentrations. Optimum stimulation of PBL was obtained 96 hr after addition of 10(-7) M TPA. TPA produced significant stimulation of PBL at concentrations of 10(-8)-10(-6) M with peak responses occurring after 3-5 days. TPA nonselectively stimulated T cells and B cells. PHAP and ConA stimulated predominantly T cells. In mixed lymphocyte reactions pretreatment of either the responder T cells or stimulating allogeneic cells with TPA inhibited DNA synthesis. Cells activated by TPA (or supernatant from these cells) suppressed proliferative response by autologous T and B cells to allogeneic cells or mitogens. TPA induced formation of T cells bearing IgG-Fc receptors and T cells forming autologous erythrocyte rosettes. TPA evidently induces suppressor T cells or T cell subsets required for suppressor activity. TPA actively suppressed the activity of natural killer (NK) cells and killer cells effecting antibody-dependent cellular cytotoxicity (ADCC). TPA should be useful for studies of suppressor mechanisms, NK activity, and ADCC. (64 Refs)

39. A PHORBOL ESTER (TPA) CAN REPLACE MACROPHAGES IN HUMAN LYMPHOCYTE CULTURES STIMULATED WITH A MITOGEN BUT NOT WITH AN ANTIGEN.

Koretzky GA, Daniele RP, Nowell PC
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J Immunol; 128(4):1776-1780 1982

A culture system was developed in which human peripheral blood mononuclear cells (PBM) depleted of macrophages did not proliferate in response to the lectin mitogen PHA or to the soluble antigen of tetanus toxoid. These cells were able to respond to both mitogen and antigen if purified autologous macrophages were added back to the culture. The response to PHA was partially restored by supplementing the cultures with supernatants from LPS-stimulated macrophages or with partially purified human interleukin 1 (IL 1). The response to tetanus was not restored by reconstitution with these materials. The phorbol ester, 12-O-tetradecanoyl-phorbol-13-acetate (TPA), has been shown to have IL 1-like effects in other species and is a polyclonal activator of human T and B lymphocytes. In this study, we tested the ability of TPA to replace macrophages in human lymphocyte cultures stimulated with mitogen or with antigen. Small doses of TPA (50 ng/ml) completely replaced macrophages in the PHA-stimulated cultures; however, in doses of up to 400 ng/ml, TPA was not able to replace macrophages in cultures stimulated with tetanus. Thus, TPA appears to mimic the macrophage-replacing ability of soluble factors (IL 1, macrophage supernatants) in the triggering of human lymphocytes. (Author abstract) (31 Refs)

40. TUMOUR-PROMOTING DITERPENE ESTERS PREVENT MACROPHAGE ACTIVATION.

Keller R, Keist R, Hecker E
Immunobiology Res. Group, Inst. Immunology and Virology, Univ. Zurich, 8032 Zurich, Switzerland
Br J Cancer; 45(1):144-146 1982

Peritoneal wash-outs from normal DA rats or C3H/J mice were interacted for 8 hr with macrophage-activating lymphokines. 14C-Deoxythymidine-labeled DA rat polyoma-induced tumor cells were interacted with effector cells for 36 hr at 37 C; the released radioactivity was measured and net cytotoxicity calculated. The phorbol esters 12-O-tetradecanoyl-phorbol-13-acetate (TPA), phorbol-12,13-didecanoate (PDD), and the 1alpha-alkyldaphnane, Pimelea factor P2, were similarly active in preventing lymphokine-induced or spontaneous enhancement of macrophage tumoricidal activity. Manifestation of macrophage cytotoxicity was inhibited whether or not effector cells were first pretreated for 4 hr with tumor promoters and the washed effector cells interacted with prelabeled targets, or the promoting agents were present throughout the entire 36-hr effector/target cell interaction. Thus, active tumor promoters of the phorbol diester- and daphnane-type prevent lymphokine-induced enhancement of macrophage cytolysis; such a capacity to suppress activation or manifestation of cytotoxicity by rat and mouse macrophages may be common to all tumor promoters. Tumor promoters may facilitate the outgrowth of transformed cells by stimulation of their multiplication and functional capacities and by suppression of the host's cellular antitumor effector systems. (11 Refs)

41. EFFECT OF MACROPHAGES ON PHORBOL ESTER STIMULATED COMITOGENESIS IN BOVINE LYMPHOCYTES.

Mastro AM, Pepin KG
Microbiology and Cell Biology Program, Dept. Microbiology, Pennsylvania State Univ., University Park, PA, 16802
Cancer Res; 42(5):1630-1635 1982

12-O-Tetradecanoylphorbol-13-acetate (TPA) added together with mitogenic lectins to bovine lymph node lymphocytes causes a synergistic increase in DNA synthesis. This comitogen effect is due to an increase in cell proliferation. To determine the role of macrophages in comitogenesis, lymphocyte preparations were depleted of macrophages by sequential adherence to glass, plastic, and nylon wool. Phagocytic cells were removed

by incubation with carbonyl iron and a magnet. After macrophage depletion, the lymphocyte response to lectins decreased, indicating the accessory function of macrophages in mitogenesis. The addition of TPA or macrophages to the depleted cultures restored its response to that of the unfractionated cells. TPA was still comitogenic with lectin in lymphocyte preparations from which all residual macrophages were removed by antimacrophage serum and complement. Therefore, the comitogenic effect of TPA is independent of macrophages in these cultures. (Author abstract) (38 Refs)

42. TUMOR PROMOTOR PHORBOL MYRISTIC ACETATE IS A T-CELL-DEPENDENT INDUCER OF IMMUNOGLOBULIN SECRETION IN HUMAN LYMPHOCYTES.

Ralph P, Kishimoto T
Developmental Hematopoiesis, Memorial Sloan-Kettering Cancer Center, Rye, NY, 10580
Clin Immunol Immunopathol; 22(3):340-348 1982

Human peripheral blood mononuclear cells were induced by 10 to 200 ng/ml phorbol myristic acetate (PMA) to secrete immunoglobulin (Ig). Using protein A-RBC plaque formation to detect secreting cells (PFC), Day 5 and Day 7 PFC induced by PMA were 0.2 to 1.4% of initial numbers of cultured cells. In parallel cultures, pokeweed mitogen (PWM) induced PFC corresponding to 1-3% and 0.6-8% of initial cell numbers, respectively. Suppressor cells for Ig secretion purifying with T (E-rosetting) cells were found in most donors. These were sensitive to mitomycin C. In some donors, PFC responses could only be detected after removal of suppressor cells. By double separation of T cells from B cells, the PMA response was shown to be dependent on T helper cells, similarly to PWM. This is in contrast to a 20-fold stimulation of Ig secretion in some human B culture lines by PMA alone. PMA is thus a T-dependent polyclonal activator for resting, blood B lymphocytes, and a direct stimulator of Ig production in certain dividing lymphoblasts represented by B-cell lines. (Author abstract) (28 Refs)

43. PHORBOL ESTER-INDUCED DIFFERENTIATION OF A NON-T, NON-B LEUKEMIC CELL LINE: MODEL FOR HUMAN LYMPHOID PROGENITOR CELL DEVELOPMENT.

LeBien TW, Bollum FJ, Yasmineh WG, Kersey JH
Dept. Lab. Medicine and Pathology, Univ. Minnesota, Box 609 Mayo, Minneapolis, MN, 55455
J Immunol; 128(3):1316-1320 1982

The phorbol ester 12-O-tetradecanoylphorbol-13-acetate (TPA) was tested for its ability to induce phenotypic changes in the human non-T, non-B ALL cell line REH. Cells were cultured with nanogram concentrations of TPA for up to 48 hr, and were analyzed by indirect immunofluorescence with a panel of monoclonal antibodies and an antibody to the enzyme terminal deoxynucleotidyl transferase (TdT). TPA induced REH cells to express the leukemia-associated antigen, p24 (detected with monoclonal antibody BA-2; p24/BA-2) by 8 hr of culture, with induction complete by 24 hr. TPA-treated cells also underwent a concomitant decrease in the expression of TdT when analyzed enzymatically or by immunofluorescence. Analysis of TPA-treated cells with monoclonal antibodies BA-1 (detecting a B cell-associated antigen), 7.2 (detecting a monomorphic HLA-DR antigen), or OKT11 (detecting a structure closely associated with the E receptor) showed no change compared to controls. In addition there was no detectable cytoplasmic immunoglobulin in control or TPA-treated cells. These results show clearly that TPA is capable of inducing phenotypic changes in REH cells. Such changes may reflect the differentiation-linked expression of antigens present in normal bone marrow lymphoid progenitor cells. (Author abstract) (41 Refs)

44. INDUCTION OF MATURATION IN CULTURED HUMAN MONOCYTIC LEUKEMIA CELLS BY A PHORBOL DIESTER.

Tsuchiya S, Kobayashi Y, Goto Y, Okumura H, Nakae S, Konno T, Tada K
Dept. Pediatrics, Tohoku Univ. Sch. Medicine, Sendai 980, Japan
Cancer Res; 42(4):1530-1536 1982

Suspension cultures of a human monocytic leukemia cell line, THP-1, were treated with 0.16 to 160 nM 12-O-tetradecanoylphorbol-13-acetate (TPA). In an original cell line, THP-1-O, c ultured again from-80 C cryopreservation, more than 80% of the cells adhered to the glass substrate with marked morphological change within 3 hr of TPA treatment. Adherent cells became flat and ameboid in shape, and many microvilli and flaps of the cell surface disappeared. Well-developed Golgi apparatus, rough endoplasmic reticula, and a large amount of free ribosomes were seen in the cytoplasm. On the other hand, in THP-1-R cells cultured continuously without cryopreservation for 26 mo, approximately 80% of the cells adhered to the substrate 48 hr after TPA treatment. Round and ovoid shapes were kept in THP-1-R cells treated with TPA. Surface Fc receptors for immunoglobulin G were present on more than 90% of THP-1-O and THP-1-R cells and were little affected by treatment with TPA. Sixty to 70% of the TPA-treated THP-1-O and THP-1-R cells were able to phagocytize yeasts and immunoglobulin G-coated sheep erythrocytes. Less than 20% of the untreated THP-1 cells were able to phagocytize yeasts and immunoglobulin G-coated sheep erythrocytes. In histochemical staining, alpha-naphthyl butyrate esterase was enhanced after treatment with TPA. Lysozyme activity in culture supernatants was not affected by TPA treatment. When exposed to latex beads and TPA, increased 14CO2 production from [1-14C]glucose in THP-1-O cells was observed. These results indicate that, after treatment with TPA, human monocytic leukemia cells may be converted into mature cells with functions of macrophages. (Author abstract) (24 Refs)

45. MODIFICATION BY SERUM OF DIFFERENTIATION OF CULTURED HUMAN MYELOID LEUKEMIA CELLS IN RESPONSE TO 12-O-TETRADECANOYLPHORBOL-13-ACETATE.

Honma Y, Kasukabe T, Hozumi M
Dept. Chemotherapy, Saitama Cancer Center Res. Inst., Ina-machi, Kitaadachi-gun, Saitama-ken 362, Japan
Gan; 73(1):97-104 1982

In medium with serum, 12-O-tetradecanoylphorbol-13-acetate (TPA) induced alpha-naphthyl acetate esterase activity in human promyelocytic leukemia cells (HL-60), adherence of the cells to the culture dish, and their change into forms that were morphologically similar to macrophages. HL-60 cells grew in the absence of serum in synthetic medium supplemented with insulin, transferrin, and several trace elements, and could be maintained for more than 6 mo in this medium. Induction of differentiation by TPA was observed with cells grown in serum-free medium. Human myeloid leukemia cells (K562-4) cultured in medium with serum could not be induced to differentiate even in the presence of TPA, but their differentiation into macrophages in the presence of TPA, arginase or actino-

mycin D was observed after they had been grown in serum-free medium for 4 mo. Addition of serum inhibited the induction of differentiation of HL-60 and K562-4 cells that had been grown in serum-free medium. Calf serum was more inhibitory than fetal calf serum on TPA-induced differentiation, but there was no significant difference in the effects of the two sera on induction by actinomycin D or arginase. These results suggest that the different responses in media with different sera may be specific to TPA. Induction of adhesiveness of K562-4 cells by TPA required some unknown serum factor(s), although addition of serum inhibited the inductions of morphological and functional differentiation. The relation between the ability of K-562-4 cells to be induced to differentiate into macrophages and long-term cultivation in serum-free medium is discussed. (Author abstract) (18 Refs)

46. ORNITHINE DECARBOXYLASE: ESSENTIAL IN PROLIFERATION BUT NOT DIFFERENTIATION OF HUMAN PROMYELOCYTIC LEUKEMIA CELLS.

Luk GD, Civin CI, Weissman RM, Baylin SB
Oncology Center, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD, 21205
Science; 216(4541):75-77 1982

The ornithine decarboxylase inhibitor DL-alpha-difluoromethyl ornithine inhibited a proliferation-associated increase in ornithine decarboxylase activity in cultured human promyelocytic leukemia cells, resulting in a marked suppression of cell proliferation and subsequent cell loss. It also inhibited increases in ornithine decarboxylase activity associated with the phorbol ester-induced conversion of promyelocytic HL-60 cells to monocyte-like cells and the retinoic acid-induced conversion to granulocyte-like cells. However, the inhibition of ornithine decarboxylase activity did not prevent cellular differentiation. These results suggest that polyamine biosynthesis has a specific role in cell proliferation rather than in inducing differentiation that is not accompanied by proliferation. The data also demonstrate that cessation of proliferation in HL-60 cells is not necessarily associated with differentiation. (Author abstract) (18 Refs)

EPIDEMIOLOGIC DATA CONCERNING MODIFICATION OF CARCINOGENESIS

47. CANCER RESEARCH IN THE PEOPLE'S REPUBLIC OF CHINA AND THE UNITED STATES OF AMERICA. EPIDEMIOLOGY, CAUSATION AND NEW APPROACHES TO THERAPY. PROCEEDINGS OF A CONFERENCE HELD IN NEW YORK, 28-29, MARCH, 1980.

Marks PA
Memorial Sloan-Kettering Cancer Center, New York, NY
Cancer Research in the People's Republic of China and the United States of America. Epidemiology, Causation and New Approaches to Therapy, Proceedings of a Conference held in New York, 28-29, March, 1980. New York, Grune and Stratton, 273 pp., 1981.

Cancer (CA) epidemiology, causation, diagnosis, and therapy are discussed. An overview of CA research, needs and opportunities of evolving perspectives on the epidemiology of CA, a national survey of CA mortality in China, geographic patterns of CA in the United States, and progress of CA epidemiology in China are presented. The study of a virus-related protein in human breast CA, the nature o f CA cells, potential carcinogens in the diet of individuals at high risk for esophageal CA, association of the Epstein-Barr virus with nasopharyngeal carcinoma (CR), aspects of research studies on liver CR, the mechanisms of action of carcinogens and tumor promoters and their relevance to CA prevention, immunological studies of esophageal CA in man, and nasopharyngeal CR epidemiology, risk factors and screening for early detection are presented. Recent progress in antineoplastic drug research in China, gene amplification in methotrexate resistant cells, and studies on harringtonine as a new antitumor drug are discussed. Advances in the study of CA epidemiology, biology, and therapy in the laboratories are offering new options for the prevention and treatment of CA. The substantive exchanges among scientists of these countries provide data useful for CA research and treatment. (365 Refs)

REVIEWS AND OTHER RELATED STUDIES

48. THE NATURAL HISTORY OF NEOPLASTIC DEVELOPMENT: THE RELATION OF EXPERIMENTAL MODELS TO HUMAN CANCER.

Pitot HC
McArdle Lab. Cancer Res., Dept. Oncology and Pathology, Medical Sch., Univ. Wisconsin, Madison, WI, 53706
Cancer; 49(6):1206-1211 1982

The natural history of the development of neoplasia in experimental systems may be separated into at least three different stages, those of initiation, promotion and progression. Evidence for such distinct stages has been demonstrated in at least half a dozen different experimental systems. The stage of promotion is that stage most easily modulated. The actions of promoting agents are reversible and only effective above certain threshold levels of the promoting agent. This is in contrast to the stage of initiation, which can be induced at any dose of the carcinogenic agent in an irreversible manner. Agents exhibiting both initiating and promoting activities are termed complete carcinogens while incomplete carcinogens are those capable only of initiation. Promoting agents do not initiate but may promote cells initiated by ambient environmental means, giving the appearance of complete carcinogens in standard bioassay procedures. The stages of initiation and promotion have been extensively studied in skin and liver carcinogenesis and show almost identical characteristics. A variety of promoting agents in the human environment have been demonstrated both by experimental and epidemiologic methodologies. The importance of an understanding of tumor promotion in relation to the prevention of human cancer is emphasized. (Author abstract) (38 Refs)

49. THE NATURE OF CANCER CELLS.

Dulbecco R
Salk Inst., La Jolla, CA
Cancer Research in the People's Republic of China and the United States of America: Epidemiology, Causation and New Approaches to Therapy, Proceedings of a Conference held in New York, 28-29, March, 1980. Marks PA, ed. New York, Grune and Stratton, 273 pp., 1981.

Differences between cancerous and normal cells, ectopic hormones and other proteins, specific cancer changes, cancer markers as replication markers, causes of the majority of irregularities of gene expression in cancer cells, viral carcinogenesis, mechanism of transformation, the transforming gene, genetic events of chemical carcinogenesis, regulation of gene expres-

sion in development, initiation, promotion, differentiation, mechanism of the derangement of gene expression in cancer - the role of promotion, other events in progression, a model for carcinogenesis, and consequences of the model are discussed. (43 Refs)

50. THE MECHANISM OF ACTION OF CARCINOGENS AND TUMOR PROMOTERS AND THEIR RELEVANCE TO CANCER PREVENTION.

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Div. Environmental Sciences, Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032

Cancer Research in the People's Republic of China and the United States of America: Epidemiology, Causation and New Approaches to Therapy, Proceedings of a Conference held in New York, 28-29, March, 1980. Marks PA, ed. New York, Grune and Stratton, 273 pp., 1981.

Systems for studying malignant cell transformation in vitro, mimicry of transformation, modulation of differentiation, membrane effects and phospholipid metabolism, membrane receptors for epidermal growth factor and 12-O-tetradecanoyl-phorbol-13-acetate (TPA), synergistic interactions between chemical agents and viruses in cell transformation, molecular mechanism of initiation, and a unified theory of initiation and promotion are discussed. Examples of cell culture systems that can be transformed by chemical carcinogens and by TPA modulation of differentiation are presented. (61 Refs)

51. STUDIES ON THE MECHANISMS INVOLVED IN MULTISTAGE CARCINOGENESIS IN MOUSE SKIN.

Slaga TJ, Fischer SM, Weeks CE, Klein-Szanto AJ, Reiners J

Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830

J Cell Biochem; 18(1):99-119 1982

Skin tumors can be induced in mice by repeated applications of a carcinogen (complete carcinogenesis) or one subthreshold dose of a carcinogen followed by repeated applications of a weak or noncarcinogenic tumor promoter (initiation-promotion carcinogenesis). Of several mouse strains studied, Sencar was the most sensitive to both types of carcinogenesis. An important aspect of tumor initiation by polycyclic aromatic hydrocarbons (PAH) is their metabolism to an electrophilic intermediate(s) which interacts covalently with epidermal DNA. Tumor promotion can be divided into at least two stages: the first obtainable by limited treatment with 12-O-tetradecanoylphorbol-13-acetate (TPA) or certain nonpromoters; the second obtainable by repeated applications of mezerein. The dark basal keratinocytes (primitive stem cells) are important in the first stage of promotion. Most of the other cellular and biochemical events associated with promotion are actually associated with the second stage. Some evidence has been found suggesting that strain and/or stock differences in responses to complete and/or multistep carcinogenesis represent differences in responses to complete and/or promotion. Although C57BL/6 mice are relatively resistant to PAH initiation and phorbol ester promotion, they are fairly sensitive to complete carcinogenesis by PAH, suggesting that this strain is resistant to phorbol ester tumor promotion. Sencar and C57BL/6 mice seem to respond qualitatively but not quantitatively to one application of TPA. (97 Refs)

52. TUMOR PROMOTION BY REGENERATIVE EPIDERMAL HYPERPLASIA IN MOUSE SKIN.

Argyris TS

Dept. Pathology, Upstate Medical Center, State Univ. New York, Syracuse, NY, 13210

J Cutan Pathol; 9(1):1-18 1982

Chemically induced epidermal carcinogenesis is usually divided into two stages: initiation, which involves the conversion of epidermal cells into latent neoplastic cells; and promotion, which allows the expression of this neoplastic change. One of the characteristics of promotion is the transformation of the normal epidermis into a hyperplastic epidermis. One of the unanswered questions about epidermal tumor promotion is whether the epidermal hyperplasia that characterizes promoted skin is simply a regenerative epidermal hyperplasia resulting from damage produced by the promoter. The opinion currently held is that the epidermal hyperplasia produced by tumor promoters is not simply a regenerative epidermal hyperplasia and possesses characteristics which a regenerative hyperplasia does not have, enabling it to evolve into an epidermal neoplasm. The purpose of this review is to present recent evidence which strongly suggests that promoter induced hyperplasia is a regenerative hyperplasia. Two principal lines of evidence are reviewed. Th first demonstrates that an epidermal regenerative hyperplasia repeatedly produced by wounding or abrasion can promote epidermal carcinogenesis in the initiated skin of mice. The second line of evidence demonstrates that the epidermal hyperplasia produced by the application of 12-0-tetradecanoylphorbol-13-acetate (TPA), the most powerful and widely used promoter of skin carcinogenesis, is preceded by damage to the epidermis. This strongly suggests that the epidermal hyperplasia which ensues is a regenerative hyperplasia. The review concludes that during epidermal tumor promotion there is a chronic regenerative epidermal hyperplasia, and that there is no evidence for any other necessary factors during tumor promotion in appropriately initiated mouse skin. (Author abstract) (36 Refs)

53. SOLAR RADIATION AND MALIGNANT MELANOMA OF THE SKIN.

Houghton AN, Viola MV

Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021

J Am Acad Dermatol; 5(4):477-483 1981

Solar radiation is discussed in relation to the pathogenesis of malignant melanomas (MM) of the skin. The incidence of MM in relatively homogeneous white populations in North America, northern Europe, and Australia is inversely proportional to latitude. MM tends to occur on sites more heavily exposed to sun during recreation. MM is more likely to develop in lightly pigmented individuals. Susceptible persons who have lived in a sunny climate all of their lives have a higher incidence of MM than persons who have recently moved to the same area from less sunny climates. A higher incidence of MM seems to occur in areas with extensive coastlines. MM is more frequent in the summer. MM rates are considered in terms of indoor and outdoor occupations. Sunspot cycles seem to be correlated with subsequent increases in MM incidence rates. Max sunspot numbers coincide with periods of increased solar activity. The rise in MM incidence 0-3 yr after sunspot peaks suggests that heavier exposures to UV radiation trigger the clinical appearance of MM. Solar radiation is considered as a dose-dependent carcinogen and as a cocarcinogen or promoter. (34 Refs)

54. BILE ACIDS AND CARCINOMA OF THE LARGE BOWEL.

Raedsch R
Innere Medizin IV, Medizinische Universitatsklinik, Bergheimer Strasse 58, 6900 Heidelberg, W. Germany
Inn Med; 9(1):8-15 1982

Possible correlations between high-fat diets, increased concentration of bile acids in the intestines, and the development of cancer of the colon are discussed. The following aspects of these correlations are considered: metabolism of bile acids, animal models for a relationship between bile acids and colon cancer, bile acids and intestinal bacteria, carcinogenic, cocarcinogenic, and procarcinogenic activities of bile acids, clinical significance of bile acids, and relationship between bile acids and dietary fiber. (74 Refs) (In GER)

55. SEX HORMONES AND LIVER CANCER.

Williams GM
Naylor Dana Inst. for Disease Prevention, New York Medical Coll., Valhalla, NY
Lab Invest; 46(3):352-354 1982

The ability of hormones to produce tumors in endocrine-related organs of experimental animals and the phenomenon of two-stage carcinogenesis is reviewed. Liver tumor promotion, mechanisms of promotion, and the potential impact of use of estrogen-containing drugs on cancer development are discussed. The fact that human exposure to several promoters (eg phenobarbital and dichlorodiphenyl trichloroethane) does not appear to cause increased occurrence of liver neoplasms may mean that the agents were not present at high levels or for prolonged continuous exposure sufficient to impede cell-cell communication and thus promoting activity. (41 Refs)

56. ANTITUMOR EFFECT OF RETINOIDS.

Mahrle G, Berger H
Universitats-Hautklinik, v. Siebold-Str. 3, D-3400 Gottingen, W. Germany
Z Hautkr; 57(6):429,430,433 1982

The potential value of retinoids in the treatment of skin tumors is discussed. Experiments in animals have shown that high doses of retinoids have antitumor effects against malignancies induced by viruses, chemicals, ionizing radiation, and UV radiation. It is noted that these experiments also revealed that extremely high doses of retinoids can cause promotion of tumor growth. This cocarcinogenic effect was most pronounced with UV-radiation induced tumors; doses as low as 0.01% and 0.001% have been reported to enhance tumor growth. In rabbits treated topically with dimethylbenzanthracene (DMBA), 20-30 mg of aromatic retinoids per day per animal was found to inhibit tumor growth. Despite the experimental findings, retinoids are not widely used in the treatment of human cancer. It is suggested that they could be valuable in the treatment of basal cell carcinoma, squamous cell carcinoma, and melanoma. It is concluded that retinoids will be used in the future as adjuvant therapy for reducing the size of tumors or preventing recurrences. (15 Refs) (In GER)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO MAN. SOME ANTINEOPLASTIC AND IMMUNOSUPPRESSIVE AGENTS.
Schmahl D
International Agency for Cancer Research, Lyon, France
IARC Mongr Eval Carcinog Risk Chem Hum 26: 411 pp., 1981.

2. BIOCHEMICAL TOXICOLOGY OF BENZENE.
Snyder R, Longacre SL, Witmer CM, Kocsis JJ, Andrews LS, Lee EW
Dept. Pharmacology, Thomas Jefferson Univ., Philadelphia, PA, 19107
Rev Biochem Toxicol; 3:123-153 1981

3. A REVIEW OF THE MUTAGENICITY OF CHROMIUM.
Hatherill JR
Toxicology, Sch. Public Health, Univ. Michigan, Ann Arbor, MI, 48109
Drug Chem Toxicol; 4(3):185-195 1981

4. HORMONES AND BREAST CANCER.
Pike MC, Siiteri PK, Welsch CW
Dept. Family and Preventive Medicine, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033
Banbury Rep 8: 491 pp., 1981.

5. ORAL CONTRACEPTIVES: VOLUME 5.
Briggs MH, Briggs M
Deakin Univ., Geelong 3217, Australia
Oral Contraceptives: Volume 5. St. Albans, VT, Eden Medical Research Inc., Annual Research Reviews--Endocrinology, 331 pp., 1981.

6. EPIDEMIOLOGICAL STUDIES OF THE ROLE OF EXOGENOUS ESTROGENS IN THE ETIOLOGY OF BREAST CANCER.
Kelsey JL, Bulbrook RD, Korenman SG, Siiteri PK, Henderson BE
Dept. Epidemiology and Public Health, Yale Univ. Sch. Medicine, New Haven, CT, 06510
Banbury Rep; 8:215-228 1981

7. EFFECTS OF LONG-TERM EXPOSURE TO LOW LEVELS OF OZONE: A REVIEW.
Melton CE
Civil Aeromedical Inst., Federal Aviation Admin., Oklahoma City, OK, 73125
Aviat Space Environ Med; 53(2):105-111 1982

8. METABOLIC INTERACTIONS OF HYDROCARBONS WITH MAMMALIAN LUNG.
Smith BR, Bend JR
Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, NIH, Research Triangle Park, NC, 27709
Rev Biochem Toxicol; 3:77-122 1981

9. REVIEW OF EXPERIMENTAL CARCINOGENESIS BY COMPOUNDS RELATED TO VINYL CHLORIDE.
Chu KC, Milman HA
NCI, Bethesda, MD, 20205
Environ Health Perspect; 41:211-220 1981

10. REVIEWS IN BIOCHEMICAL TOXICOLOGY.
Hodgson E, Bend JR, Philpot RM
North Carolina State Univ., Raleigh, NC
Rev Biochem Toxicol 3: 368 pp., 1981.

DIETARY FACTORS IN CARCINOGENESIS

11. ALCOHOL AND CANCER.
MacSween RN
Univ. Dept. Pathology, Western Infirmary, Glasgow, Scotland
Br Med Bull; 38(1):31-33 1982

12. THE TOXICOLOGY OF COCOA AND METHYLXANTHINES: A REVIEW OF THE LITERATURE.
Tarka SM
Life Sciences, Hershey Foods Corp., Corporate Technical Center, Hershey, PA
CRC Crit Rev Toxicol; 9(4):275-312 1982

13. IMPLICATIONS OF DIETARY FIBER BREAKDOWN IN THE HUMAN COLON.
Cummings JH, Stephen AM, Branch WJ
MRC Dunn Clinical Nutrition Centre, Old Addenbrookes Hosp., Cambridge, CB2 1QE, England
Banbury Rep; 7:71-81 1981

14. BILE SALTS AND OTHER CONSTITUENTS OF THE COLON AS TUMOR PROMOTERS.
Reddy BS, Tannenbaum SR, Montesano R, Correa P, Haenszel W, Wattenberg LW
Div. Nutrition, American Health Foundation, Naylor Dana Inst. for Disease Prevention, Valhalla, NY, 10595
Banbury Rep; 7:345-363 1981

15. MOLD PRODUCING CARCINOGENIC TOXINS IN FOOD PRODUCTS.
Preda N
Institutul de medicina si farmacie, Cluj-Napoca, Romania
Rev Chir [Oncol]; 20(1):1-9 1981
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16. THE MEANING OF CANCER 'DIETS'.
Jungi WF
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MMW; 124(2):26-28 1982
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EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

17. RISK FACTORS FOR CERVICAL CANCER.
Hulka BS
Dept. Epidemiology, Rosenau Hall 201H, Univ. North Carolina, Chapel Hill, North Carolina, NC, 27514
J Chronic Dis; 35(1):3-11 1982

18. EPIDEMIOLOGY OF THE MOST FREQUENTLY OCCURRING TUMORS OF THE DIGESTIVE SYSTEM.
Naujoks-Heinrich S, Dolle W
Abteilung Innere Medizin I, Universitatsklinik, Otfried-Muller-Strasse 10, D-7400 Tubingen, W. Germany
Internist (Berlin); 23(1):1-9 1982
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19. BLADDER CANCER.
Skrabanek P, Walsh A
Endocrine Oncology Unit, Mater Misericordiae Hosp., Dublin, Ireland
UICC Tech Rep Ser 60: 192 pp., 1981.

20. RECENT ADVANCES IN CANCER CYTOGENETICS.
Pogosiants EE
All-Union Cancer Res. Center, Moscow, USSR
Genetika; 17(12):2087-2099 1981
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21. CURRENT STATUS OF CYTOGENETIC STUDIES IN ANIMAL TUMORS WITH SPECIAL REFERENCE TO NONRANDOM CHROMOSOME CHANGES.
Sasaki M
Chromosome Res. Unit, Hokkaido Univ., Faculty Science, Sapporo 060, Japan
Cancer Genet Cytogenet; 5(2):153-172 1982

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

22. ASBESTOS-RELATED DISEASES.
Casey KR, Rom WN, Moatamed F
Building 512, RMCOEH, Univ. Utah Medical Center, Salt Lake City, UT, 84112
Clin Chest Med; 2(2):179-202 1981

23. NONASBESTOS FIBROUS MINERALS.
Lockey JE
Building 512, RMCOEH, Univ. Utah Medical Center, Salt Lake City, UT, 84112
Clin Chest Med; 2(2):203-218 1981

24. REVIEW OF EPIDEMIOLOGIC STUDY RESULTS OF VINYL CHLORIDE-RELATED COMPOUNDS.
Apfeldorf R, Infante PF
Office Carcinogen Identification and Classification, Health Standards, Programs, Occupational Safety and Health Admin. U. S. Dept. Labor, Washington, DC, 20210
Environ Health Perspect; 41:221-226 1981

25. CONCEPTS IN CAUSALITY: CHEMICALLY INDUCED HUMAN URINARY BLADDER CANCER.
Lower GM
Center Human Systems, Inst. Environmental Studies, Univ. Wisconsin, WARF Building, 610 Walnut St., Madison, WI, 53706
Cancer; 49(5):1056-1066 1982

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

26. MOLECULAR MECHANISM OF ADAPTATION OF CELLS TO LOW LEVELS OF CARCINOGENIC AGENTS.
Villani G
Laboratoire de Pharmacologie et de Toxicologie Fondamentales, CNRS, 205, route de Narbonne, 31078 Toulouse Cedex, France
Pathol Biol (Paris); 30(2):117-123 1932
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27. MIGHT CANCER BE A FAILED RESPONSE TO RENEGADE MITOCHONDRIA?
Hartung J
Dept. Anesthesiology, State Univ. New York, Downstate Medical Center, Brooklyn, NY, 11203
J Theor Biol; 94(1):173-178 1982

MODIFICATION OF CARCINOGENESIS

28. EFFECT OF GEROPROTECTORS ON CARCINOGENESIS.
Anisimov VN
N. N. Petrov Res. Inst. Oncology, Leningrad, USSR
Usp Sovrem Biol; 92(3):455-472 1981
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29. RELATION OF NEUROLEPTIC DRUGS TO DEVELOPMENT AND GROWTH OF MAMMARY TUMORS.
Meites J, Aylsworth CF
Dept. Physiology, Neuroendocrine Res. Lab., Michigan State Univ., East Lansing, MI, 48824
Banbury Rep; 8:365-376 1981

30. THE ACTIONS OF INSULIN AS A HORMONAL FACTOR IN BREAST CANCER.
Hilf R, Siiteri PK, Shellabarger, Korenman SG, Rosen, Nandi
Dept. Biochemistry and Univ. Rochester Cancer Center, Univ. Rochester, Rochester, NY, 14642
Banbury Rep; 8:317-337 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

31. ONCOGENES.
Bishop JM
Univ. California, San Francisco, CA
Sci Am; 246(3):80-84,87-92,154 1982

32. HUMAN CANCERS AND HUMAN VIRUSES.
Waterson AP
Royal Postgraduate Medical Sch., London W12 0HS, England
Br Med J; 284(6314):446-448 1982

33. THE IMMUNOLOGY OF CANCER OF THE HEAD AND NECK WITH PARTICULAR REFERENCE TO ORAL CANCER.
Scully C
Univ. Dept. Oral Medicine and Pathology, Immunology Unit, Glasgow Dental Hosp., 378 Sauchiehall St., Glasgow G2 3JZ, Scotland
Oral Surg; 53(2):157-169 1982

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34. THE USE OF MAMMALIAN CELL MUTANTS TO STUDY THE MECHANISMS OF CARCINOGENESIS.
Trosko JE, Chang CC, Warren ST, Liu PK, Wade MH, Tsushimoto G
Dept. Pediatrics and Human Development, Michigan State Univ., Coll. Human Medicine, East Lansing, MI, 48824
Gann Monogr Cancer Res; 27:159-179 1982

35. BIOLOGICAL MONITORING IN THE IDENTIFICATION OF THE CANCER RISK OF INDIVIDUALS EXPOSED TO CHEMICAL CARCINOGENS.
Vainio H, Sorsa M, Rantanen J, Hemminki K, Aitio A
Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
Scand J Work Environ Health; 7(4):241-251 1981

36. A CRITICAL REVIEW OF BIOLOGICAL METHODS FOR THE DETECTION OF FUNGAL TOXINS IN FOODS AND FOODSTUFFS.
Watson DH, Lindsay DG
Food Science Div., Ministry of Agriculture, Fisheries, and Food, Great Westminster House, Horseferry Road, London SW1P 2AE, England
J Sci Food Agric; 33(1):59-67 1982

37. PITUITARY AND STEROID HORMONES IN RADIATION-INDUCED MAMMARY TUMORS.
Shellabarger CJ
Medical Dept., Brookhaven National Lab., Upton, NY, 11973
Banbury Rep; 8:339-351 1981

38. ASPERGILLUS NIDULANS: SYSTEMS AND RESULTS OF TESTS FOR CHEMICAL INDUCTION OF MITOTIC SEGREGATION AND MUTATION. I. DIPLOID AND DUPLICATION ASSAY SYSTEMS. A REPORT OF THE U. S. EPA GE NE-TOX PROGRAM.
Kafer E, Scott BR, Dorn GL, Stafford R
Dept. Biology, McGill Univ., 1205 Ave. Docteur Penfield, Montreal H3A 1B1, Canada
Mutat Res; 98(1):1-48 1982

OTHER REVIEWS IN CARCINOGENESIS

39. MATHEMATICAL MODELS OF THE CELL CYCLE WITH A VIEW TO TUMOR STUDIES.
Bertuzzi A, Gandolfi A, Giovenco MA
Centro di Studio dei Sistemi di Controllo e Calcolo Automatici del C.N.R., Via Eudossiana 18, 00184 Roma, Italy
Math Biosci; 53(3/4):159-188 1981

40. NEOPLASMS IN DOMESTIC ANIMALS: A REVIEW OF EXPERIMENTAL AND SPONTANEOUS CARCINOGENESIS.
Madewell BR

Section Clinical Oncology, Dept. Veterinary Surgery, Univ. California, Davis, CA, 95616

Yale J Biol Med; 54(2):111-125 1981

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SERIES CK04 No. 82/09 SEPTEMBER, 1982

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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HE 20.3173/2:

MODIFICATION OF CARCINOGENESIS BY CHEMICAL AGENTS OR IRRADIATION

1. EFFECT OF DIAZEPAM ON HEPATOCARCINOGENESIS IN THE RAT.

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Toxicol Lett; 11(1/2):155-157 1982

The tumor promoting ability of diazepam on the number and size of enzyme altered islands (EAI) in rat liver was investigated. Ten male Donryu rats were fed a diet containing 500 ppm diazepam (50 mg/kg/day) after initiation with 0.06% 3'-methyl-4-(dimethylamino)-azobenzene. Liver tissue was subsequently examined for ATPase-deficient islands (greater than 50 microns in diameter) at wk 16. Mean EAI values in the treated group were 8.64/square cm, compared to control values of 9.76/square cm. Diazepam induced neither cytomegaly nor reduction of canalicular ATPase activity in the centrolobular hepatocytes. Diazepam is apparently not a tumor promoter like phenobarbital. (14 Refs)

2. ORGAN-SPECIFIC PROMOTING EFFECTS OF PHENOBARBITAL SODIUM AND SODIUM SACCHARIN IN THE INDUCTION OF LIVER AND URINARY BLADDER TUMORS IN MALE F344 RATS.

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JNCI; 68(3):497-500 1982

Studies were conducted to determine whether initial treatment with N-2-fluorenylacetamide (2-FAA) or N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) followed by treatment with either phenobarbital sodium (PB) or sodium saccharin (SS) induced or enhanced liver and/or bladder tumorigenesis. Male inbred F344 rats were given 0.05% PB and 5.0% SS in the diet for 32 wk after 4-wk administration of 0.02% 2-FAA or 0.01% BBN. PB significantly enhanced hepatocarcinogenesis after 2-FAA treatment and induced hyperplastic liver nodules after BBN treatment. The SS significantly enhanced induction of bladder hyperplasias, but not papilloma after BBN treatment, and induced bladder hyperplasias after 2-FAA treatment. However, PB had no effect on the bladder and SS had no effect on the liver after either 2-FAA or BBN treatment. The data indicate that although 2-FAA and BBN have tumor-initiating effects in the liver and urinary bladder, the tumor-promoting effects of PB and SS are organ-specific. The tumor-promoting effect of PB for the liver is relatively greater than that of SS for the urinary bladder. (Author abstract) (25 Refs)

3. RESPIRATORY TRACT TUMOURS IN HAMSTERS EXPOSED TO ACETALDEHYDE VAPOUR ALONE OR SIMULTANEOUSLY TO BENZO(A)PYRENE OR DIETHYLNITROSAMINE.

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Eur J Cancer Clin Oncol; 18(1):13-31 1982

Syrian golden hamsters were exposed to 0 or 2,500-1,650 ppm acetaldehyde vapor, 7 hr/day, 5 days/wk for a period of 52 wk. A proportion of the animals was given, simultaneously, either intratracheal instillations of benzo(a)pyrene (BP) or sc injections of diethylnitrosamine (DENA). All treatments were stopped after 52 wk. The study was terminated after 81 wk. Major effects attributed to acetaldehyde exposure included growth retardation, rhinitis, hyperplasia and metaplasia of the nasal, laryngeal and tracheal epithelium, nasal and laryngeal carcinomas, and a markedly increased incidence of BP-initiated tracheobronchial carcinomas. There was no evidence of acetaldehyde enhancing the development of DENA-initiated tumors of the respiratory tract. It was concluded that acetaldehyde is an irritant, as well as a carcinogen, for the respiratory tract of Syrian golden hamsters. Possible mechanisms of the carcinogenicity of this aldehyde are briefly discussed. (Author abstract) (15 Refs)

4. THE KINETICS OF THE PROTECTIVE EFFECT OF BETA-SITOSTEROL AGAINST MNU-INDUCED COLONIC NEOPLASIA.

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J Cancer Res Clin Oncol; 103(1):49-54 1982

The effect of dietary supplementation with beta-sitosterol (0.2% of diet) was followed in Fischer rats after both acute and chronic feeding. Compared to controls after 3 and 7 days, the number of epithelial cells per crypt column in both plant sterol fed groups was shifted to lower values; moreover, fewer cells above cell position 12 were engaged in DNA synthesis. Continued feeding of beta-sitosterol for 28 wk revealed the number and position of 3HTdR-labeled cells per crypt column after 1 hr pulse labeling to be similar to that seen in the acute phase. However, differences were more marked after 24 hr showing the max number of labeled cells per column to be at least 25% less than the untreated group and the leading edge of labeled cells moving more slowly up the crypt wall. Rats treated with N-methyl-N-nitrosourea (MNU) intrarectally (8 mg/animal) while simultaneously consuming beta-sitosterol demonstrated a reduction in the size of the proliferative compartment as well as the number of labeled cells per crypt column as compared to rodents receiving just the carcinogen (3.3 and 5.4 mean labeled cells per column, respectively). At this time, MNU-treated rats fed beta-sitosterol had a significantly decreased colonic tumor incidence. This plant sterol which passes through the digestive tract relatively unabsorbed appears to slow colonic epithelial cell proliferation resulting in a reduced expression of neoplastic transformation. (Author abstract) (6 Refs)

5. ENHANCEMENT OF SKIN TUMORIGENESIS BY CIGARETTE SMOKE CONDENSATE FOLLOWING BETA-IRRADIATION IN RATS.

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JNCI; 68(4):605-611 1982

The tumor-promoting ability of cigarette-smoke condensate (CSC) has been demonstrated in rat skin after beta-irradiation. Skin tumors from male albino Charles River CD rats (outbred Sprague-Dawley descended) were classified into two groups: carcinomas and other noncarcinoma tumors. A statistically significant increase (p less than 0.01) in tumor yield occurred after CSC treatment that began 2 mo after irradiation. This finding confirmed our previously published pilot observation. Extension of the pilot experiment to obtain data on carcinoma yield and an experiment to observe the effects of CSC treatment beginning immediately after irradiation were performed. When

CSC treatment began immediately after irradiation, the yield of noncarcinoma tumors was significantly reduced (p less than 0.01), whereas the carcinoma yield increased but statistically not significantly (p = 0.12). The increased yield of noncarcinoma tumors is attributed to a significant increase (p less than 0.01) of acute ulceration caused by CSC on recently irradiated skin. The increase in carcinoma yield resulted from an increase in the rate of conversion of noncarcinoma tumors to cancer. Carcinoma yield was also increased by CSC treatment beginning 2 mo after irradiation, but the increase was not significant (p = 0.08). The lack of statistical significance for the carcinoma yields in both experiments may be ascribed to the insufficient number of cancers produced by the treatments. The relative ratios of cancer yields (1.7 and 2.5) did not differ greatly from the 2.2 ratio for the increase of noncarcinoma tumors. The possible relevance of the findings to human carcinogenesis is discussed. (Author abstract) (38 Refs)

MODIFICATION OF CARCINOGENESIS BY DIETARY COMPONENTS OR DIGESTIVE FACTORS

6. PROGRESSION OF CARCINOGEN-INDUCED FOCI OF GAMMA-GLUTAMYLTRANSPEPTIDASE-POSITIVE HEPATOCYTES TO HEPATOMAS IN RATS FED A CHOLINE-DEFICIENT DIET.

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Int J Cancer; 29(4):445-450 1982

Following previous findings that feeding a choline-deficient (CD) diet to rats strongly promotes the evolution of liver cells, initiated by a chemical carcinogen, to foci of gamma-glutamyltranspeptidase (gammaGT)-positive hepatocytes, we investigated whether a CD diet could also promote the evolution of gammaGT-positive foci to hepatomas. GammaGT-positive foci were induced in male Sprague-Dawley rats by administration of a single dose of diethylnitrosamine followed by 2 wk feeding on a CD diet containing 0.02% acetylaminofluorene. Immediately thereafter, one group of rats was fed a plain CD diet and the other a choline-supplemented (CS) diet, and subgroups of animals were killed periodically for analysis of the number and size of gammaGT-positive foci and development of hepatomas. During the first 7 wk after switching the diets, the number and size of the foci increased in both groups. At 12 and 16 wk, the number and size of foci began to decline in rats fed the CS diet. However, in the CD group, there was a progressive increase in the size with coalescence of the foci, as well as development of neoplastic nodules. These lesions were followed at 20 and 28 wk by development of hepatomas at a high incidence rate. In rats fed the CS diet, a few scattered gammaGT-positive foci, and small neoplastic nodules remained in the liver at 20 and 28 wk, but no hepatomas developed. These results show that the CD diet is a potent promoter of the evolution of foci of altered hepatocytes to hepatomas, and that most of the gammaGT-positive foci are reversible lesions. (Author abstract) (37 Refs)

7. PROMOTIVE EFFECTS OF STEROIDS AND BILE ACIDS ON HEPATOCARCINOGENESIS INITIATED BY DIETHYLNITROSAMINE.

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Cancer Res; 42(6):2426-2428 1982

The ability of four steroids and three bile acids to promote the appearance of hyperplastic foci and hyperplastic nodules initiated by diethylnitrosamine (DEN) in the liver of male Fischer rats was tested and compared with that of the known promoter phenobarbital (PB, 0.05%) as a standard value. Two weeks after a single dose of 200 mg of DEN per kg, the animals were exposed to test chemicals for 10 weeks. At 4 weeks following DEN, all treatment groups were subjected to partial hepatectomy. Of the steroids tested at the maximum tolerable doses, as determined in preliminary experiments, ethinyl estradiol was the most potent promoter, inducing more hyperplastic nodules than did PB and almost 50% less gamma-glutamyl transpeptidase-positive foci. However, gamma-glutamyl transpeptidase-positive foci induced by ethinyl estradiol were twice the average size as those induced by PB. The steroids testosterone, cortisone, and dexamethasone induced more foci than did DEN alone, but few if any hyperplastic nodules. Deoxycholic acid was the most potent promoter of the bile acids tested, inducing 3 to 4 times more hyperplastic nodules than did PB and more gamma-glutamyl transpeptidase-positive foci, which were 5 times larger on the average than those induced by PB. The other bile acids tested, lithocholic acid and taurine, induced slightly more foci than did DEN alone but no hyperplastic nodules. These findings suggest that ethinyl estradiol and deoxycholic acid are relatively strong promoters of the appearance of preneoplastic lesions in hepatocarcinogenesis. (Author abstract) (22 Refs)

8. BILE ACIDS: EFFECTS ON ABSORPTION OF 1,2-DIMETHYLHYDRAZINE AND 7,12-DIMETHYLBENZ[A]ANTHRACENE IN THE COLON OF THE RAT AND GUINEA PIG.

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JNCI; 68(4):619-622 1982

The specific effects of bile acids as cocarcinogens were investigated. Absorptions of [14C]7,12-dimethylbenz[a]anthracene, [14C]dimethylhydrazine ([14C]DMH), and [3H]inulin from loops of colons from outbred Sprague-Dawley rats and Hartley guinea pigs were determined. In each animal absorption of one carcinogen and inulin was studied in one control loop and in a experimental loop containing either deoxycholic acid (DOC) or chenodeoxycholic acid (CDOC). DOC had a more pronounced effect on increasing loss of carcinogen from the intestinal lumen than did CDOC. This role of bile acids was consistent with their known effect of increasing intestinal permeability. Less carcinogen remained in the colon mucosa when DOC was present in the intestinal lumen. Although [14C]DMH was absorbed more rapidly from the intestinal lumina of guinea pigs than from those of rats, the rat accumulated more of the carcinogen in the intestinal mucosa and liver. (Author abstract) (16 Refs)

9. GLUTATHIONE S-TRANSFERASE ACTIVITY: ENHANCEMENT BY COMPOUNDS INHIBITING CHEMICAL CARCINOGENESIS AND BY DIETARY CONSTITUENTS.

Sparnins VL, Venegas PL, Wattenberg LW
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JNCI; 68(3):493-496 1982

Benzyl isothiocyanate, beta-naphthoflavone, coumarin, alpha-angelicalactone, disulfiram, indole-3-carbinol and indole-3-acetonitrile induced increased (GSH) glutathione S-transferase activity in the liver and small intestine in female ICR/Ha mice. All seven compounds are inhibitors of chemical carcinogenesis. In additional work, several dietary constituents increased GSH S-transferase activity. Consumption of diets containing dried powdered preparations of brussel sprouts, cabbage, coffee beans, or tea leaves resulted in increased GSH S-transferase activity. Mice fed an unrefined diet (Purina Rat Chow) had a higher GSH S-transferase activity than those fed a semipurified diet. The results of the present study indicated that the composition of the diet can alter the activity of an important enzyme system having the capacity to detoxify chemical carcinogens. (Author abstract) (28 Refs)

10. INHIBITION OF CHEMICAL CARCINOGENESIS BY RETINOIDS.

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J Am Acad Dermatol; 6(4 part2):809-814 1982

Experiments involving two-stage skin carcinogenesis in mice, the induction of bladder tumors in rats or mice by N-methyl-N-nitrosourea (MNU) or N-butyl-N-(4-hydroxybutyl)nitrosamine (OH-BBN), the induction of mammary tumors in rats by MNU, and the induction of esophageal tumors in rats by N-methyl-N-benzylnitrosamine have demonstrated several important structure-activity relationships in the inhibition of chemical carcinogenesis by retinoids. The aromatic ring, side chain, and polar terminal groups of the retinoid molecule have important effects on the agent's organ distribution and thus its anticarcinogenic activity. Retinoids that significantly inhibit OH-BBN bladder carcinogenesis include 13-cis-retinoic acid (c-RA), ethyl retinamide, 13-cis-ethyl retinamide, 2-hydroxyethyl retinamide, 4-hydroxyphenyl retinamide (4-HPR), 13-cis-4-hydroxyphenyl retinamide, and 2-hydroxypropyl retinamide. Retinoic acid (RA) is a less favorable preventer of MNU-induced mammary tumors in rats than 4-HPR, because 4-HPR accumulates to a lesser extent in the liver and so is less hepatotoxic than RA. Synergistic interactions between retinoids (eg, RA or 4-HPR) and hormonal treatments in MNU mammary carcinogenesis have been discovered. Retinoid treatment from the time of carcinogen administration or the first excision of a carcinogen-induced tumor has greater chemopreventive activity than delayed treatment. The efficacy of delayed retinoid treatment largely depends on the tumor's latent period. The authors' current research involves the identification of new retinoids having lower toxicity and higher chemopreventive activity, combination treatments having synergistic antitumor activity, and the mechanisms of action of the retinoids. (28 Refs)

11. ORAL MUCOSAL CARCINOGENESIS IN HAMSTERS: INHIBITION BY VITAMIN E.

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JNCI; 68(5):791-797 1982

Eighty young adult male and female Syrian golden hamsters (Mesocricetus auratus) were divided into four equal experimental groups. In Group 1 animals the left buccal punch was painted 3x weekly with a 0.5% solution of 7,12-dimethylbenz[a]anthracene (DMBA) in heavy mineral oil. In Group 2 animals the left buccal pouch was similarly painted with DMBA, but the animals also received orally 10 mg vitamin E (dl-alpha-tocopherol) in peanut oil twice weekly on alternate days with the DMBA painting. Group 1 animals received a similar amount of peanut oil vehicle, Group 3 animals received only vitamin E (vitamin E controls) in peanut oil, and Group 4 animals served as untreated controls receiving only peanut oil. Four animals in each group (2 males and 2 females) were killed at 8, 10, 12, 14, and 16 wk. Buccal pouches were photographed and excised, and tumors were noted and measured in the left buccal pouches. In Group 2 animals receiving vitamin E, tumor formation was significantly delayed, so that by 14-16 wk there were fewer tumors and their av size was smaller than that of tumors in Group 1 animals that were painted with DMBA but received no vitamin E supplement. In Group 2 there was also less invasion of underlying tissues and less surface necrosis. (Author abstract) (30 Refs)

12. EFFECT OF ASCORBIC ACID ON THE CARCINOGENIC ACTIVITY OF P-HYDROXYPHENYLLACTIC ACID.

Khar'kovskaia NA, Khrustalev SA, Zharova EI, Raushenbakh MO
Dept. Experimental Animals, All-Union Cancer Res. Center, Moscow, USSR

Biull Eksp Biol Med; 92(1):64-66 1982

Anticarcinogenic effect of ascorbic acid (AA) during carcinogenesis induced by tyrosine metabolites was studied in C57BL mice. The animals were divided into two groups: mice in Group 1 received para-hydroxyphenyllactic acid alone (PHPLA: 5 mg, sc 2x/wk, 5 wk), and mice in Group 2 received the PHPLA in combination with AA (250 mg/100 ml in drinking water). The animals were followed up for 20-22 mo. Tumors were observed in 55% of the mice in Group 1 and in 22.5% of those in Group 2. Most tumors in both groups had histologies of mixed lymphosarcoma. In addition to the lymphosarcoma, mice in Group 1 developed bladder precancer and hyperplasia, while mice in Group 2 were free of bladder precancer and had an incidence of hyperplasia of bladder epithelium which was 3x lower than that in Group 1. The AA administration increased the latent period of tumor development. (8 Refs) (In RUS)

MODIFICATION OF CARCINOGENESIS BY HORMONAL OR GENETIC FACTORS

13. EFFECTS OF HYPOTHYROIDISM ON DEVELOPMENT OF NITROSOMETHYLUREA-INDUCED TUMORS OF THE MAMMARY GLAND, THYROID GLAND, AND OTHER TISSUES.

Milmore JE, Chandrasekaran V, Weisburger JH
(c/o Weisburger) American Health Foundation, Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595
Proc Soc Exp Biol Med; 169(4):487-493 1982

Female Fischer 344 rats were injected iv with 50 mg/kg N-nitrosomethylurea (NMU) at 50 days of age; some also received 0.3, 1.0, or 3.0 mg propylthiouracil (PTU) per 100 ml of drinking water, beginning 5 days after the NMU administration, and others received 131I injections. Six wk after treatment, serum thyroxine levels were elevated in rats receiving NMU only, but not in those receiving PTU as well, whereas a 10 uCi dose of 131I caused a slight but significant depression of serum thyroxine level. PTU or 131I increased the incidence of benign and 1 malignant mammary tumors, except in rats receiving the highest PTU dose, which had a decreased incidence of malignancies. Weights of ovaries, uteri, or adrenal glands were unaffected by NMU or PTU. Malignant neoplasms were adenocarcinomas that were sometimes multiple. Benign thyroid tumors were follicular adenomas; malignant thyroid tumors were mostly follicular, or follicular mixed with papillary carcinoma. Numerous other neoplasms appeared in other systems. Slight hypothyroidism could increase the incidence of NMU-induced mammary tumors in the rat, but when hypothyroidism was severe enough to limit growth, tumor incidence was less. (32 Refs)

MODIFICATION OF CARCINOGENESIS BY VIRUSES, BACTERIA OR IMMUNE SYSTEM COMPONENTS

14. LYMPHOTOXIN ENHANCES THE SUSCEPTIBILITY OF NEOPLASTIC AND PRENEOPLASTIC CELLS TO NATURAL KILLER CELL MEDIATED DESTRUCTION.

Ransom JH, Evans CH
Tumor Biology Section, Lab. Biology, Div. Cancer Cause and Prevention, NCI, Bethesda, MD, 20205
Int J Cancer; 29(4):451-458 1982

Treatment of neoplastic guinea-pig cells for 1-14 days with 300 units of guinea-pig lymphotoxin/ml medium enhanced two- to five-fold their susceptibility to natural killer (NK) cell-mediated cytotoxicity as measured by 4 hr 51Cr and 72 hr [3H]-thymidine-release assays. The NK susceptibility of human neoplastic and guinea-pig non-neoplastic cells refractory to guinea-pig lymphotoxin growth-inhibitory activity was unchanged after lymphotoxin treatment. Lymphotoxin preparations were free of detectable interferon and the enhancing activity copurified with lymphotoxin during diafiltration and isoelectric focusing. Treatment of NK cells with lymphotoxin preparations also augmented NK-mediated lysis but that activity did not copurify with lymphotoxin. As with neoplastic cells, lymphotoxin-sensitive preneoplastic cells previously treated with ultraviolet light, a chemical carcinogen, or carcinogen and the tumor-promoting agent tetradecanoyl-phorbol-acetate also exhibited lymphotoxin enhancement to NK-cell destruction. Thus, the immunologic hormone lymphotoxin enhances the susceptibility of lymphotoxin-sensitive cells to NK-cell destruction, indicating that these two natural immune mediators, lymphotoxin and NK cells, have the potential in concert to regulate carcinogenesis and neoplastic growth. (Author abstract) (30 Refs)

15. MURINE LEUKEMIA. PROPOSED ROLE FOR GANGLIOSIDES IN IMMUNE SUPPRESSION.

Krishnaraj R, Lengle EE, Kemp RG
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Eur J Cancer Clin Oncol; 18(1):89-98 1982

Glycolipid-bound sialic acid levels were elevated two to four-fold in the sera of two strains of mice bearing thymic lymphoma produced either spontaneously (AKR/J) or due to chemical carcinogenesis [Swiss mice injected with 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboximide]. The serum glycolipid-bound sialic acid level reflected the tumor burden of the AKR/J mice during the early stages of leukemogenesis. Furthermore, the elevation was found to coincide with the ontogenesis of thymic lymphoma and not to be simply an age-dependent phenomenon. TLC analysis of Florisil column-purified gangliosides from the sera of AKR/J and Swiss mice suggested presence of gangliosides with mobilities very close to GM2 and GM3 standards respectively. On the premise that the elevated glycolipid levels in circulation might interfere with normal lymphocyte functions, the immunoinhibitory properties of exogenously added mixed gangliosides were examined on tests of in vitro correlates of the immune response. Gangliosides inhibited concanavalin A and lipopolysaccharide-induced [3H]-thymidine, [14C]-leucine and [5H]-lysine uptake by normal AKR/J mouse thymocytes and spleen cells. Mixed gangliosides also suppressed the two-way mixed lymphocyte reaction of AKR/J x Swiss and AKR/J x DBA/2 spleen cells. These and other results strongly suggest a general immunologically relevant role for gangliosides in the ontogeny of thymic lymphoma of mice. (Author abstract) (39 Refs)

OTHER STUDIES OF THE MODIFICATION OF CARCINOGENESIS

16. INFLUENCES OF AGE AND ANATOMICAL SITE ON ULTRAVIOLET CARCINOGENESIS IN BALB/C MICE.

Ebbesen P, Kripke ML
(c/o Kripke) Cancer Biology Program, NCI-Frederick Cancer Res. Facility, P.O. Box B, Frederick, MD, 21701
JNCI; 68(4):691-694 1982

Young adult BALB/c mice were more susceptible to the induction of skin tumors from FS40 sunlamps than were 18-mo-old animals. The relative contributions of tissue and host factors to this difference in susceptibility to carcinogenesis were analyzed by reciprocal grafting of skin between young and old animals, followed by repeated exposures of the grafts to UV radiation. More tumors developed in ear skin grafted to the middorsum of young recipients than in that of old recipients, regardless of the age of the skin donor. These ear skin grafts were more susceptible to tumor induction that were comparable grafts of back skin. When large areas of dorsal skin (16 cm2) were grafted to young adult mice, very old skin (greater than 2 yr) was more susceptible to tumor induction than skin

that was 1 yr old at the start of irradiation. (Author abstract) (13 Refs)

17. SURGICAL RESECTION OF THE RAT COLON: EFFECTS ON CARCINOGENESIS BY 1,2-DIMETHYLHYDRAZINE.

Rubio CA, Nylander G
Dept. Pathology, Karolinska Sjukhuset, Box 60500, Stockholm, Sweden S-104 01
JNCI; 68(5):813-815 1982

Following a 3-month treatment with 1,2-dimethylhydrazine (DMH) given weekly (sc), outbred Sprague-Dawley rats were subjected to partial resection of the transverse colon. After surgery, DMH treatment was continued for 6 months, after which the rats were killed. At autopsy, 63% of the tumors were found in the transverse colon. By contrast, only 29% of the tumors found in the 'sham-operated' control animals occurred in the transverse colon. Surgical trauma in the colon mucosa subjected to the action of carcinogenic agents appeared to promote the conditions suitable for the development of tumors in that organ. (Author abstract) (16 Refs)

STUDIES OF TUMOR PROMOTION OR COCARCINOGENESIS IN MOUSE SKIN

18. A POSSIBLE IN VIVO SKIN MODEL FOR TUMOUR PROMOTER ASSAYS.

Armuth V, Berenblum I
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Cancer Lett; 15(3):343-346 1982

An improved technique for utilizing the weak carcinogenicity of [3H]thymidine (THY) as a transplacental initiator, using fractionated low-doses during several days, is described. Female and male BALB/c mice were used. Skin papilloma (SP) development in initiated-promoted mothers and their offspring was examined. THY alone, in the administered doses, was not carcinogenic for skin either in the parent mice or in the offspring. Subsequent anthranil promotion resulted in SP development in both groups. By wk 20 of promotion, cumulative SP incidence in the initiated-promoted mothers was 25%, while in offspring (both sexes) the value reached 19%. Anthranil treatment alone did not induce any SP, and the spontaneous incidence of skin tumors was nil. Individual tumor yield did not rise above one per SP-bearing mouse. A few mice with lung adenomas or liver tumors were found in the various THY-treated groups, but the incidence was unaffected by subsequent anthranil treatment. The results indicate that THY can act effectively as a transplacental initiator in mice, inducing dormant tumor cells in skin, and apparently in a variety of other organs in the fetus. Subsequent promotion might thus result in tumor development in the relevant organ, according to the promoter used. (6 Refs)

19. POLYAMINE BIOSYNTHESIS AND SKIN TUMOR PROMOTION: INHIBITION OF 12-O-TETRADECANOYLPHORBOL-13-ACETATE-PROMOTED MOUSE SKIN TUMOR FORMATION BY THE IRREVERSIBLE INHIBITOR OF ORNITHINE DECARBOXYLASE ALPHA-DIFLUOROMETHYLORNITHINE.

Takigawa M, Verma AK, Simsiman RC, Boutwell RK
McArdle Lab. Cancer Res., Univ. Wisconsin, Madison, WI, 53706
Biochem Biophys Res Commun; 105(3):969-976 1982

Topical application of alpha-difluoromethylornithine (DFMO) to shaved mouse skin or administered in the drinking water in conjunction with the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA), inhibited the formation of 7,12-dimethylbenz(a)anthracene-initiated skin papillomas. Application of 10 nanomoles of TPA to mouse skin led to a rapid and transient induction of epidermal ornithine decarboxylase (ODC) activity. Application of 1.37 umoles DFMO 1 hr after TPA to mouse skin inhibited ODC induction by nearly 100%. DFMO also resulted in significant inhibition of induced and basal levels of putrescine, while spermidine-induction was inhibited by only 20%. DFMO administered in the drinking water (1% wt/vol) beginning 3 days before and continuing through the experimental period inhibited TPA-induced increases in ODC by 100%, basal putrescine levels by 40%, and induced putrescine levels by 90%; spermidine levels were somewhat decreased, but spermine levels remained unchanged. DFMO inhibited the formation of DMBA-initiated and TPA-promoted skin papillomas by 50% when administered on the skin, and by 90% when administered in the drinking water. These results indicate an essential role for the products of ODC in TPA promotion of carcinogenesis. (22 Refs)

20. RETINOIDS AND INHIBITION OF ORNITHINE DECARBOXYLASE ACTIVITY.

Boutwell RK, Lowe NJ, DeLuca LM, Meyskens FL, McGuire JS, Krueger GG, Goldsmith LA, Kligman AM
McArdle Lab. for Cancer Res., Univ. Wisconsin, Madison, WI, 53706
J Am Acad Dermatol; 6(4,part2):796-800 1982

A model system for production of skin tumors involves a two stage system in which the skin is first exposed to a low dose of a carcinogen (initiator) which has an irreversible effect on epidermal stem cells. The second step involves exposure of skin to agents, which although not carcinogenic, will cause many tumors quickly (promoter). The second agent causes increased somatic cell gene activity, in this case, induction of ornithine decarboxylase (ODC) activity. The tumor promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA) caused a dose dependent induction of ODC activity in mouse skin within 5 hr of a skin application of 1-10 nanomoles. Induction was inhibited by a single application of from 0.034-3.4 nanomoles of retinoic acid (RA) immediately before or after TPA treatment. Of 30 retinoids tested, all trans-RA was most effective. The amount of inhibition of ODC induction was dependent on time of application of RA relative to time of TPA application, and was also correlated with dose and RA structure. A permanently increased level of ODC and its product, putrescine, may be an important component of tumor promotion. (18 Refs)

21. EFFECT OF RETINOIC ACID PRETREATMENT ON 12-O-TETRADECANOYLPHORBOL-13-ACETATE-INDUCED CELL POPULATION KINETICS AND POLYAMINE BIOSYNTHESIS IN HAIRLESS MOUSE EPIDERMIS.

Astrup EG, Paulsen JE
Inst. Pathology, Univ. Oslo, Rikshospitalet, Natl. Hosp., Oslo 1, Norway
Carcinogenesis; 3(3):313-320 1982

A single topical application of 17 nmol 12-O-tetradecanoylphorbol-13-acetate (TPA) to the skin of hairless mice induces characteristic transient alterations in the epidermal cell turnover and maturation (0-96 hr), associated in time with characteristic changes in the activities of L-ornithine carboxy-lyase (EC 4.1.1.17) (ODC) and S-adenosyl-L-methionine carboxy-lyase (EC 4.1.1.50) (SAM-D) and in the accumulation of polyamines. The effects on these responses of local pretreatment of the skin with retinoic acid 1 hr prior to TPA were investigated at selected time points. Retinoic acid inhibited the TPA-induced ODC activity and the ensuing accumulation of putrescine, but did not alter the TPA-induced SAM-D activity or the molar ratio of spermidine/spermine. This pretreatment also decreased the number of dividing basal cells in the first TPA-induced synchronized wave of proliferating cells. However, during the subsequent period of proliferation, the number of dividing cells in the retinoic acid pretreated group was comparatively increased. Hence, at four dose levels of retinoic acid (0.17, 1.70, 17.0 and 170 nmol), which all inhibited the TPA-induced ODC effectively, there was no change in the total number of basal cells that divided during 16-48 hr after TPA-application. The theory is put forward that retinoic acid might exert its antitumorigenic effect during tumor promotion with TPA by interfering with the rate and/or quality of epidermal cell maturation, rather than by inhibiting cell proliferation. (Author abstract) (62 Refs)

22. DECREASED ACCUMULATION OF CYCLIC ADENOSINE 3',5'-MONOPHOSPHATE IN 'ISCHEMIC' SKIN AFTER 12-O-TETRADECANOYL-PHORBOL-13-ACETATE TREATMENT.

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Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
J Invest Dermatol; 78(4):264-266 1982

The effect of 12-O-tetradecanoyl-phorbol-13 acetate (TPA) on cyclic adenosine 3',5'-monophosphate (cyclic AMP) level in adult mouse skin in response to ischemia was examined. The incubation of skin pieces in a buffered salts medium at 37 C resulted in a rapid accumulation of cyclic AMP. In mouse skin pieces max accumulation (about 6x the basal level) occurred after 2 min incubation and was followed by a rapid decline in the cyclic AMP level. This 'ischemic' rise in epidermal cyclic AMP was greatly reduced if skin was used 16 hr after a single application of 17 nmoles of TPA. The effect of TPA on cyclic AMP accumulation in response to ischemia was first observed at 1 hr after TPA treatment and was maximal at 4 hr. The lack of 'ischemic' response in TPA-treated skin was not related to an increase in the activity of cyclic AMP phosphodiesterase after TPA application. In addition, the accumulation of cyclic AMP in skin in response to both ischemia and exposure to isoproterenol, adenosine, histamine, or prostaglandin E2 was not observed in skin treated with the tumor promoter TPA. (Author abstract) (19 Refs)

CELL CULTURE STUDIES OF MECHANISMS OF MODIFICATION

23. DIVERGENT RESPONSES IN EPIDERMAL BASAL CELLS EXPOSED TO THE TUMOR PROMOTER 12-O-TETRADECANOYLPHORBOL-13-ACETATE.

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In Vitro Pathogenesis Section, NCI, Bethesda, MD, 20205
Cancer Res; 42(6):2344-2349 1982

Mouse epidermal basal cells can be selectively cultivated in medium with 0.02 to 0.09 mM Ca++ and can be induced to differentiate by medium containing 1.2 mM Ca++. Basal cell cultures were studied to determine if all cells in this population responded identically to the skin tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA). Studies on the induction of the enzyme epidermal transglutaminase by TPA demonstrated a two- to four-fold increase in activity within 12 hr of exposure. This activity increase paralleled morphological differentiation in approx 50% of the basal cell population, and differentiating cells sloughed from the culture dish within 24 to 48 hr as transglutaminase activity returned to basal levels. The cells which remained were resistant to induced differentiation by 1.2 mM Ca++ medium, in that they failed to demonstrate increased transglutaminase activity or decreased thymidine incorporation, both characteristics of control basal cells induced to differentiate by 1.2 mM Ca++. Cells remaining after a single exposure to TPA did not respond to a second exposure with an induction of transglutaminase if the interval between exposures was 4 days. TPA-pretreated cells did not undergo a transient decrease in thymidine incorporation (characteristic of control cells) when exposed to TPA a second time but instead were directly stimulated to proliferate by the phorbol ester, indicating that such cells were not refractory to the promoter. When the treatment-free interval after TPA was extended from 4 to 10 days, transglutaminase inducibility was restored in basal cells to either TPA or 1.2 mM Ca++ as inducers. These results indicate that heterogeneity exists within the epidermal cell population and that exposure to phorbol esters induces differentiation in some cells, while stimulating proliferation in others. Such heterogeneous responses would cause a selective redistribution of the epidermal cell population and could lead to clonal expansion of initiated cells. (Author abstract) (34 Refs)

24. GANGLIOSIDE CHANGES INDUCED BY TUMOR PROMOTERS IN PROMOTABLE JB6 MOUSE EPIDERMAL CELLS: ANTAGONISM BY AN ANTIPROMOTER.

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JNCI; 68(3):469-473 1982

Since cell surface gangliosides have been implicated in the regulation of cell growth and differentiation and since tumor-promoting phorbol esters produce a number of membrane changes, the possibility was investigated that ganglioside changes may play a role in promotion of transformation in JB6 mouse epidermal cells. The studies showed that tumor-promoting but not non-promoting phorbol esters produced decreased precursor incorporation into trisialoganglioside GT and increased incorporation into disialoganglioside GD1b and an unknown ganglioside, Gx. These ganglioside responses to promoters were antagonized by the antipromoter retinoic acid,

thus suggesting that alterations in ganglioside levels may be involved in promotion of transformation. (Author abstract) (34 Refs)

25. A NEW TUMOR-PROMOTING AGENT, DIHYDROTELEOCIDIN B, MARKEDLY ENHANCES CHEMICALLY INDUCED MALIGNANT CELL TRANSFORMATION.

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Lab. Molecular Carcinogenesis, NCI, Bethesda, MD, 20205
Science; 216(4545):527-529 1982

Teleocidin, which was isolated from mycelia of Streptomyces, is a potent tumor promoter in mouse skin. The catalytically hydrogenated compound dihydroteleocidin B markedly enhanced cell transformation induced by 3-methylcholanthrene or ultraviolet radiation. Dihydroteleocidin B was at least 100x more effective in enhancing transformation than 12-O-tetradecanoyl phorbol-13-acetate, the strongest promoter known until now, whereas both promoters showed equal capacities to induce early membrane effects and DNA synthesis. (Author abstract) (24 Refs)

26. ISOLATION OF METHYLCHOLANTHRENE-'INITIATED' C3H/10T1/2 CELLS BY INHIBITING NEOPLASTIC PROGRESSION WITH RETINYL ACETATE.

Mordan LJ, Bergin LM, Budnick JE, Meegan RR, Bertram JS
Dept. Experimental Therapeutics, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Carcinogenesis; 3(3):279-285 1982

A clone of 3-methylcholanthrene-treated 10T1/2 cells has been isolated which possess basic characteristics expected of 'initiated' cells. In the presence of retinyl acetate, this clone exhibits contact inhibited growth control and is morphologically indistinguishable from the parental 10T1/2 cell line. Removal of retinyl acetate in vitro results in neoplastic transformation after a latent period of 3 wk. The classical 10T1/2 transformation system was reconstructed by coculturing normal and 'initiated' 10T1/2 cells. In these cultures 62% of the clonogenic 'initiated' 10T1/2 cells formed either Type III foci after a latent period of 3-4 wk, and an additional 22% formed Type I foci. Treatment of 'initiated' 10T1/2 cells with the tumor promoter 12-O-tetradecanoylphorbol-13-acetate accelerated the formation of transformed foci in the coculture system by reducing the length of the latent period to less than 3 wk. Injection of 10(6) 'initiated' cells/mouse sc into nude mice resulted in the appearance of progressively growing fibrosarcomas after a latent period of 5-7 wk. Dietary supplementation with 4-hydroxyphenyl-retinamide prevented tumor formation; after drug withdrawal, tumors developed in all surviving mice after 6 wk. We believe this cell line possess all characteristics expected of 'initiated' cells. With this new cell line, designated INIT/10T1/2, we can now study the early biochemical changes in growth control mechanisms resulting in neoplastic transformation and the mechanism(s) of chemoprevention of cancer by vitamin A. (Author abstract) (31 Refs)

27. ACTIVATION OF NON-EXPRESSED BOVINE PAPILLOMA VIRUS GENOMES BY TUMOUR PROMOTERS.

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Nature; 296(5858):675-677 1982

Following infection of mouse embryo fibroblasts (MEF), bovine papilloma virus type 1 (BPV-1) genome resides in a non-expressed episomal state. After passaging of the BPV-1 infected cells, the viral DNA is eventually lost due to failure to replicate, as shown by hybridization of the viral DNA to a BPV-1 DNA probe according to the Southern method. When BPV-1-infected MEF cells were treated with the tumor promotor 12-O-tetradecanoylphorbol-13-acetate (TPA), considerably more BPV-1 DNA was found after 4 days than in the non-treated cells. Even when TPA was administered to cells in the passage 3 after infection, viral DNA could be detected while none was detectable in non-treated passage 3 cells. Viral DNA was detected at passages 1 and 5 after TPA removal, indicating that BPV-1 DNA continues to replicate in the absence of TPA. TPA also promoted viral transcription. While no viral RNA sequences could be detected in untreated MEF cells one passage after infection, 4 days after TPA treatment of a parallel culture, several species of BPV-1 RNA were found. The same RNA species were detected in BPV-1-induced hamster embryo fibroblasts. Similar results to TPA were obtained with 12-O-retinoylphorbol-13-acetate (RPA). In addition to induction of viral transcripts, TPA induced a transformed phenotype, expressed by an increase in saturation density of the cultures and the ability to grow in low serum medium. While several primate cell lines showed none of these effects, bovine fetal thyroid (BFT) cells did exhibit an enhanced DNA replication and a transient transcription and phenotypic transformation in the presence of TPA and RPA. Tumor promoter-treated MEF and BFT cells may provide a system for studying the amplification and expression of foreign genes inserted into a BPV-1 vector as well as a screening system for putative tumor-promoting agents. (22 Refs)

28. MURINE LEUKEMIA VIRUS-MEDIATED TRANSFORMATION OF A MOUSE EPITHELIAL CELL LINE MMC-E.

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Cancer Res; 42(6):2407-2411 1982

Mouse embryo epithelial cells, MMC-E, were malignantly transformed in culture with MuLV derived from C3H/MCA 5 cells chemically induced by 5-iododeoxyuridine. The frequency of transformation was significantly enhanced if infection was followed by treatment with 100 ng of 12-O-tetradecanoylphorbol-13-acetate per ml. The virus-transformed cells retained their high plating efficiency in soft agar in the absence of 12-O-tetradecanoylphorbol-13-acetate and formed neoplasms in nude mice. (Author abstract) (24 Refs)

29. INDUCTION OF DIFFERENTIATION IN HUMAN PROMYELOCYTIC LEUKEMIA CELLS BY TUMOR PROMOTERS.

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J Cancer Res Clin Oncol; 103(1):17-29 1982

The prototype polyfunctional diterpene ester tumor promoter of two-step carcinogenesis in mouse skin, 12-O-tetradecanoylphorbol-13-acetate (TPA), induced differentiation of human promyelocytic leukemia cells (HL-60) in culture. Differentiation of HL-60 cells was characterized by increased phagocytosis, increased lysozyme activity (EC 3.2.1.17) in the growth medium, and changes in morphology to those characteristics of more mature cells resembling macrophages. Many

of the cells treated with TPA became aggregated, attaching firmly to culture flasks. The av intracellular myeloperoxidase activity (EC 1.11.1.7) per cell decreased during induction of differentiation by TPA. It was also found that TPA enhanced, rather than inhibited, differentiation of HL-60 cells induced by DMSO. In addition to TPA, several polyfunctional diterpene esters of the tigliane, ingenane, and daphnane type have been tested for their ability to induce morphological and functional changes of HL-60 cells. The activities of the compounds to induce these changes correlated well with their activities as tumor promoters in two-step carcinogenesis in mouse skin. In particular, half the concentrations required for induction of adhesion of the cells to flasks were roughly correlated to the potency of these compounds as tumor promoters. Among the compounds tested, phorbol-12,13-didecanoate (PDD), ingenol-3-hexadecanoate, Pimelea factor P1 and Pimelea factor P2 were as active as TPA, while methyl-TPA and 4alpha-PDD were much less active. Phorbol and ingenol were totally inactive up to a concentration 10,000-fold higher than that of TPA. (Author abstract) (28 Refs)

30. ROLE OF PHOSPHOLIPASE A2 AND PROSTAGLANDIN E IN GROWTH AND DIFFERENTIATION OF MYELOID LEUKEMIC CELLS.

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Dept. Genetics, Weizmann Inst. Science, Rehovot 76100, Israel
Biochim Biophys Acta; 720(2):111-119 1982

Phospholipase A2 activity and prostaglandin E synthesis have been studied in different clones of myeloid leukemic cells, which differ in their competence to be induced to differentiate by the macrophage and granulocyte differentiation-inducing protein or the tumor promoter 12-O-tetradecanoyl phorbol-13-acetate (TPA). Clones that could be induced to differentiate by this protein showed a higher basal phospholipase A2 activity than clones that could not be induced to differentiate by this protein inducer. Cell competence to be induced to differentiate by TPA did not show this correlation, and the clone with the least ability to respond to TPA showed the lowest number of binding sites for [20-3H]phorbol 12,13-dibutyrate. Differentiation induced by the protein was accompanied by a 7-14-fold increase in prostaglandin E synthesis, whereas differentiation induced by TPA did not show this increase. Externally added prostaglandin E1 did not induce differentiation but inhibited cell proliferation and the degree of inhibition in the different clones was related to the basal phospholipase A2 activity. The results indicate that increase of prostaglandin E synthesis was not an essential pre-requisite for differentiation, that prostaglandin E seems to be involved in the inhibition of cell proliferation in association with phospholipase A2, and that the differentiation-inducing protein and TPA can induced differentiation by different pathways. The amount of basal phospholipase A2 activity was also related to previously found differences in the ability of the clones to develop desensitization to beta-adrenergic hormones or prostaglandin E1. (Author abstract) (25 Refs)

31. TUMOR PROMOTER 12-O-TETRADECANOYLPHORBOL 13-ACETATE: EFFECT ON COMPLEMENT AND EPSTEIN-BARR VIRUS RECEPTORS IN HUMAN LYMPHOBLASTOID CELL LINES.

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JNCI; 68(3):385-390 1982

The effect of the tumor promoter 12-O-tetradecanoylphorbol 13-acetate (TPA) on the C3 and Epstein-Barr virus (EBV) receptors in various human lymphoblastoid cells was investigated with the use of the erythrocyte-antibody-complement (EAC) rosette formation method and a quantitative bioassay for EBV receptors. TPA caused a significant decrease of C3 receptors in the cultures of both Raji and SB4 cells (by approximately 50% of the C3 receptors in untreated cultures at 10 ng/ml). Kinetic studies revealed that the rate of reduction was rather moderate but progressive, reaching a maximum 5 days after treatment with TPA. Kinetic studies showed that EBV receptors also decreased, similar to the reduction seen with C3 receptors after TPA treatment. The effect of TPA on the reduction of C3 receptors was observed not only in these cells but also in other EBV-positive B-cells, subclones of SB4 cells, and MOLT-4 cells. However, in an EBV-negative B-cell line, BJAB, EAC rosette formation was significantly enhanced. (Author abstract) (38 Refs)

32. MODULATION OF CHRONIC LYMPHOCYTIC LEUKEMIA CELLS BY PHORBOL ESTER: INCREASE IN IA EXPRESSION, IGM SECRETION AND MLR STIMULATORY CAPACITY.

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J Immunol; 128(5):2276-2280 1982

When cultured with 12-O-tetradecanoylphorbol 13-acetate (TPA) at a concentration of 1.6 x 10(-7) M, chronic lymphocytic leukemia (CLL) cells differentiated into mature cells of B lineage and increased their expression of surface Ia antigens when compared with cells cultured in the absence of TPA. Concurrently, TPA enhanced the ability of CLL cells to stimulate in a mixed lymphocyte reaction (MLR). The events induced in vitro by TPA that are characteristic of B cell maturation included morphologic changes, reduction in surface immunoglobulin (Ig), appearance of cytoplasmic Ig, and secretion of IgM. The increase in Ia expression and the enhanced capacity to stimulate in an MLR after incubation with TPA might also be associated with maturation of the CLL cells. The changes induced in vitro by TPA in neoplastic B cells provide new information concerning the terminal events in normal B cell differentiation. (Author abstract) (24 Refs)

33. ANTAGONISM OF CONCANAVALIN A CAPPING IN PHORBOL ESTER-ACTIVATED LYMPHOCYTES BY CALMODULIN INHIBITORS AND CERTAIN AMINO ACID ESTERS.

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Cancer Res; 42(6):2115-2120 1982

The compound 12-O-tetradecanoylphorbol-13-acetate (TPA), an effective tumor promoter in mouse skin and comitogen in bovine lymphocytes, rapidly stimulates concanavalin A-mediated cap formation in the latter cells. The ability of different phorbol derivatives to facilitate the capping reaction correlates well with their potencies as lymphocyte comitogens and as tumor-promoting agents. This effect of TPA on capping in bovine lymphocytes, which is apparent within min, is neither mimicked nor altered by dibutyryl cyclic adenosine 3':5'-monophosphate or cyclic guanosine 3':5'-monophosphate. Cytochalasin D, a microfilament-disrupting agent, inhibits cap formation, thereby suggesting the participation of microfilaments in the response. Benzoyl tyrosine ethyl ester selectively inhibits the TPA-stimulated cap formation, whereas benzoyl tyrosinamide

is inactive. A comparison of related amino acid derivatives reveals that their activities are dependent on the nature of both the amino acid side chain and the carboxyl end blocking group. Trifluoperazine and N-(6-aminohexyl)-5-chloronaphthalenesulfonamide, known inhibitors of the calmodulin-dependent processes, also selectively block the TPA-stimulated cap formation, whereas trifluoperazine sulfoxide, a less effective calmodulin antagonist, is relatively inactive. These data suggest that the stimulation of capping by TPA involves the activation of a calmodulin-dependent process which may also be regulated by the function of an esterase. (Author abstract) (32 Refs)

34. TUMOR PROMOTER STIMULATED IRREVERSIBLE BINDING OF N-METHYLAMINOAZOBENZENE TO POLYMORPHONUCLEAR LEUKOCYTE DNA.

Takanaka K, O'Brien PJ, Tsuruta Y, Rahimtula AD
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Cancer Lett; 15(3):311-315 1982

The irreversible binding of N-methylaminoazobenzene (MAB) to nuclear DNA catalyzed by guinea pig polymorphonuclear leukocytes (PMN), and the initiation of binding by 12-O-tetradecanoylphorbol-13-acetate (TPA), were studied. A 10(-6) M concentration of TPA resulted in the binding of 43.3 picomole of MAB to the DNA present in 10(7) cells. Little binding occurred in the absence of TPA. The binding was proportional to the number of PMN present. Evidence implicating the involvement of H2O2 is presented. Addition of catalase to the incubation medium reduced DNA binding of MAB by 80%. Addition of superoxide dismutase (which catalyzes the dismutation of O2-to produce H2O2) increased the binding by 30%, suggesting that the rate of H2O2 production was limiting. Addition of horseradish peroxidase (HRP), which has high affinity for H2O2, increased the binding by 75%. Since HRP cannot penetrate the PMN plasma membrane, the activation of MAB by HRP must occur outside the cell itself and the reactive intermediates are apparently sufficiently stable to penetrate the plasma membrane and interact with the DNA. The antioxidant butylated hydroxyanisole reduced the MAB bound to DNA by 90%, suggesting the involvement of free radicals in the activation process. The observation that TPA can trigger the irreversible binding of MAB to DNA suggests that it could also be involved in the initiation process. (18 Refs)

35. PROTEASE INHIBITORS FROM PROCESSED LEGUMES EFFECTIVELY INHIBIT SUPEROXIDE GENERATION IN RESPONSE TO TPA.

Yavelow J, Gidlund M, Troll W
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Carcinogenesis; 3(2):135-138 1982

Crude extracts containing protease inhibitors from edible legumes (canned chick-peas, canned kidney beans and bean curd) were capable of blocking the superoxide response of human polymorphonuclear leukocytes produced by the tumor promoter 12-O-tetradecanoyl-phorbol-13-acetate (TPA). Protease inhibitors purified from crude extracts more effectively blocked the superoxide response produced by TPA. Bowman-Birk soybean inhibitor was more effective in blocking this effect of the tumor promoter than Kunitz soybean inhibitor. The significance of protease inhibitors in edible legumes and the possible role of free oxygen radicals in tumor promotion are discussed. (Author abstract) (32 Refs)

36. SELECTIVE PROLIFERATION OF NORMAL HUMAN MELANOCYTES IN VITRO IN THE PRESENCE OF PHORBOL ESTER AND CHOLERA TOXIN.

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Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Proc Natl Acad Sci USA; 79(6,part1):2018-2022 1982

Cultures consisting almost entirely of human melanocytes were obtained from epidermal single-cell suspensions by using phorbol 12-myristate 13-acetate (10 ng/ml) in the culture medium. At this concentration, phorbol ester is toxic to human keratinocytes but not to melanocytes. When the seeding density was optimal (0.8-2 x 10(4)/cm2) and the medium contained both phorbol ester and cholera toxin, melanocytes proliferated extensively. Under these conditions, human melanocytes could be passaged serially in vitro and grown in quantity. This cell culture system can thus be used to answer basic questions related to pigment cell biology and may serve as a control for studies of malignant melanocytes. (Author abstract) (32 Refs)

37. INHIBITION OF RESPIRATION BY A PHORBOL ESTER TUMOR PROMOTER IN MURINE CULTURED CELLS.

Backer JM, Boersig MR, Weinstein IB
Div. Environmental Sciences and Cancer Center/Inst. Cancer Res., Columbia Univ., New York, NY, 10032
Biochem Biophys Res Commun; 105(3):855-860 1982

The effect upon mitochondrial function of in vitro exposure of intact murine embryo fibroblasts (C3H 10T1/2) to 12-0-tetradecanoyl phorbol-13-acetate (TPA) was investigated. Nontoxic doses of TPA induced a rapid decrease in mitochondrial respiration in both normal and carcinogen-transformed fibroblasts. Alterations in mitochondrial function may play an important role in both the initiation and tumor promotion phases of chemical carcinogenesis. (18 Refs)

38. RETINOIC ACID-PROMOTED EXPANSION OF TOTAL CELLULAR ATP POOLS IN 3T3 CELLS CAN MEDIATE ITS STIMULATORY AND GROWTH INHIBITORY EFFECTS.

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Dept. Microbiology, Boston Univ. Sch. Medicine, Boston, MA, 02118
J Cell Physiol; 110(3):318-322 1982

Levels of beta-all-trans-retinoic acid (RA) which stimulate the phorbol myristate acetate (PMA)-induced transition from resting to growing states in 3T3 cells following short periods of treatment were found to produce marked increases in total cellular ATP and uridine triphosphate pools of the resting cells. Total cellular ATP pools increased by about twofold during transition of cells from G1 phase to S phase of their cell cycle. Treatment of serum-deprived cultures with 10 uM RA for at least 48 hr prior to serum stimulation and up to the time of analysis increased total cellular ATP pools during all phases of the cell cycle. Treatment of asynchronous cells with 10 uM RA for 72 hr produced no difference in labeling indices compared to controls, despite a 40% inhibition of (3H)thymidine incorporation. Exposure of G0/G1-arrested 3T3 cells to 10 uM RA for 18 hr followed by removal of the RA-containing medium and addition of 50 nanogram/ml PMA resulted in a substantial potentiation of the mitogenic response to PMA. These results indicated that RA treatment of 3T3 cells lengthened the S phase of their cycle by reducing the rate of DNA synthesis. (21 Refs)

39. ENHANCEMENT OF HORMONE ACTION BY A PHORBOL ESTER AND ANTI-TUBULIN ALKALOIDS INVOLVES DIFFERENT MECHANISMS.

Simantov R, Sachs L
Dept. Genetics, Weizmann Inst. Science, Rehovot 76100, Israel
Biochim Biophys Acta; 720(2):120-125 1982

The tumor-promoting phorbol ester 12-O-tetradecanoyl phorbol-13-acetate (TPA) enhanced 1-isoproterenol and prostaglandin E1 stimulated cyclic AMP formation in clones of mouse myeloid leukemic cells. The enhancement was found up to 3 hr after TPA treatment and had disappeared after 24 hr, indicating its reversibility. The effect of TPA was not inhibited by removal of extracellular Ca++ or pretreatment with the calcium ionophore A23187. This enhancement by TPA seems to involve a different pathway than enhancement of response to the same hormones after treatment with the anti-tubulin alkaloids colchicine or vinblastine, since a myeloid leukemic cell mutant clone that was non-responsive to the anti-tubulin alkaloids responded to TPA. Furthermore, combined treatment of colchicine-sensitive cells with TPA and colchicine showed an additive stimulating effect. The enhancement of cell response to hormones by TPA was found in myeloid leukemic cell clones that either were or were not induced to differentiate after treatment with TPA. This suggests that enhancement of the effect of these and possibly other hormones by TPA may be an initial step of TPA action, but that this enhancement is not sufficient to induce the wide repertoire of TPA effects including induction of differentiation. (Author abstract) (36 Refs)

40. TUMOR PROMOTERS INCREASE THE SYNTHESIS OF A 32,000-DALTON PROTEIN IN BALB/C 3T3 CELLS.

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Proc Natl Acad Sci USA; 79(6,part1):1800-1804 1982

The effect of 12-O-tetradecanoylphorbol 13-acetate (TPA), a potent tumor promoter, on the synthesis of proteins in BALB/c 3T3 mouse fibroblasts has been studied. When [35S]methionine-labeled proteins synthesized after the addition of TPA were analyzed by one- or two-dimensional polyacrylamide gel electrophoresis, the increased synthesis of a 32,000-dalton protein (designated p32) was noted as one of the earliest changes. The synthesis of p32 increased approx two-fold within 2 hr at a promoter concentration of 20 ng/ml. Phorbol 12,13-didecanoate, another potent tumor promoter, showed the same effect as TPA, whereas 4-O-methyl-TPA, which has little promoting activity, did not enhance the synthesis of p32 at the same concentration but did effect a slight increase at 1 ug/ml. p32 differed immunologically from a major excreted protein discovered by Gottesman. The increased rate of the synthesis of p32 was considered to be regulated at the transcriptional level, because the increase in synthesis of p32 was inhibited by actinomycin D, and TPA-treated cells were shown to contain a higher level of translatable mRNA coding for p32 than do control cells. A possible relationship between the increase in p32 synthesis and transformation is discussed. (Author abstract) (49 Refs)

41. DIVERSE EFFECTS: AUGMENTATION, INHIBITION, AND NON-EFFICACY OF 12-O-TETRADECANOYLPHORBOL-13-ACETATE (TPA) ON RETROVIRUS GENOME EXPRESSION IN VIVO AND IN VITRO.

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Carcinogenesis; 3(3):261-265 1982

The action of 12-O-tetradecanoylphorbol-13-acetate (TPA) on several retrovirus-related functions was investigated in four virus-host cell systems. The following effects were recorded: (i) in STU-mice, infected with the Friend virus complex (Friend murine leukemia virus/Friend spleen focus forming virus) and treated with TPA (50 ng/g) for 1 wk prior to infection, the number of spleen foci increased five-fold over the control. (ii) Addition of TPA (0.04 to 40 ng/ml) to virus-producing cell systems resulted in a two-fold increase of extracellular reverse transcriptase activity. The max response was observed in Friend leukemia virus-producing mouse cells at 0.1 to 0.4 ng TPA/ml and in simian sarcoma virus-producing rat cells at 4 ng/ml. (iii) The efficiency of transformation of BalbC 3T3 cells by Moloney murine sarcoma virus, tested in a focus formation assay, was slightly enhanced by TPA. (iv) TPA inhibited the induction of endogenous virus formation in B cell mitogen-stimulated spleen cell cultures from BalbC mice. (Author abstract) (18 Refs)

EPIDEMIOLOGIC DATA CONCERNING MODIFICATION OF CARCINOGENESIS

42. DESCRIPTIVE EPIDEMIOLOGY OF CANCERS OF THE UPPER RESPIRATORY TRACT IN LOS ANGELES.

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Univ. Southern California Sch. Medicine, 2025 Zonal Ave., Los Angeles, CA, 90039
Cancer; 49(10):2201-2207 1982

The descriptive epidemiology of cancer of three upper respiratory tract sites (lip; mouth and pharynx, excluding nasopharynx; and nose, sinus and nasopharynx) was explored using data from 1972-1976 from the population-based cancer registry covering Los Angeles County, California. In addition, the proportion of Los Angeles cases at each site which are explained by tobacco use was estimated using attributable risks calculated from previously published case-control studies. Causes of non-tobacco-related cases are considered. Lip cancer was found to be a disease predominantly of white males with a male/female ratio of 9.8 for the lower lip and of 1.0 for the upper lip. Tobacco use is responsible for 60% of male lip cancers, and incidence rates of lip cancer after subtraction of the proportion of the incidence due to tobacco use were more than 3 x greater in men than in women. A hypothesis is proposed that an important etiologic factor is exposure to sun, wind and cold which results in chapping; this exposure is most intense for the lower lip; and the use of lip coverings in women protects their lips both from the sun and from chapping. Cigarette smoking was responsible for 51% of mouth and pharynx cancer in men and women in Los Angeles County, and after subtraction of the proportion of the incidence due to smoking, rates in men and women were similar. Factors such as poor dentition and nutritional deficiencies may help explain demographic characteristics such as the higher rates of mouth and pharynx cancer

among men and women in the lower social classes and the secular decline in incidence rates. Cancers of the nose, sinus and nasopharynx were found to occur among workers in a wide range of occupations and industries which involved inhalation of dust, fumes and vapors. High incidence rates of nasopharynx cancer were observed among Chinese in Los Angeles and high rates of sinus cancer among Spanish-surnamed residents. Cancers at these sites appear to be related to the action of carcinogens on tissue chronically irritated by repeated upper respiratory infections or allergic responses. In addition racial differences in the physical structure of the nasal passage may influence where inhaled particles are deposited. (Author abstract) (51 Refs)

43. LARGE BOWEL CANCER: THE NEXT MOVE?

Hughes ES, McDermott FT, Polglase AL, Johnson WR, Pihl EA
Dept. Surgery, Monash Univ., Alfred Hosp., Commercial Road, Prahran, Victoria 3181, Australia
Med J Aust; 1(1):36-37 1982

Despite an intensive anti-cancer campaign and a shorter delay between the appearance of symptoms and consultation with a physician, the survival rates for large bowel cancer (LBC) have not improved significantly. In some studies, results have actually worsenned. Prophylaxis of LBC requires the detection of people who are more likely to develop carcinoma of the large bowel. A tendency for certain families to be affected by the disease has been observed although no predictable pattern has been discerned. Patients who have had a LBC successfully removed are at greater risk of developing a second new primary tumor. Benign tumors are very common in the human colon. Diagnosis and treatment of such polyps are described. Untreated, familial polyposis of the large bowel develops into malignancy. The incidence of LBC is much higher in patients with ulcerative colitis than in the general community. Factors possibly related to LBC, such as low residue diet, high beef (particularly fried) diet, water chlorination particularly in areas deficient in selenium, occupational hazards, and other environmental factors, must be determined and eliminated. (16 Refs)

REVIEWS AND OTHER RELATED STUDIES

44. MUTAGENS, CARCINOGENS, AND TUMOR PROMOTERS IN OUR DAILY FOOD.

Sugimura T
Natl. Cancer Res. Inst., Tsukiji, Chuo-ku, Tokyo, Japan
Cancer; 49(10):1970-1984 1982

Identification of mutagens, carcinogens, tumor promoters in human food is reviewed. Studies of the food additive 2-(2-furyl)-3-(5-nitrofuryl)acrylamide, which is mutagenic in the Ames test and produced tumors in mice, indicated that if a compound in food shows mutagenicity, its carcinogenicity should be considered and that data obtained on mutagenicity prior to 1960 may be invalid. Improvement and adoption of the Ames test for screening for carcinogens in food are discussed. Isolation and identification of new heterocyclic amines from pyrolysates of amino acids, proteins, and proteinous foods are described. Mutagens and carcinogens in edible plants, vegetables, fruits, alcoholic spirits, spices, and beverages are described. Tumor promoters are discussed in relation to life style. Recommendations are proposed for cancer prevention. (159 Refs)

45. NUTRITION AND CANCER: MECHANISMS OF GENOTOXIC AND EPIGENETIC CARCINOGENS IN NUTRITIONAL CARCINOGENESIS.

Weisburger JH, Horn C
American Health Foundation, Valhalla, NY, 10595
Bull NY Acad Med; 58(3):296-312 1982

Mechanisms of carcinogenesis are reviewed with regard to type of chemical carcinogen - genotoxic, cocarcinogen, or promoter. Examples and mode of action are given for each. The role of epigenetic agents in nutritionally linked cancers, particularly large bowel or colon cancer, is discussed; specific dietary elements considered relevant through studies in human and animal models are the amount of dietary fat and fiber and mode of cooking. The operation of these elements is through epigenetic mechanisms, which are dose and time dependent. A reduction in dose should lead to lowering of risk, which may eventually be applied to humans through dietary adjuvant therapy. (71 Refs)

46. CARCINOGENIC EFFECT OF RADIOACTIVE PRODUCTS.

Vasilenko IIa
No affiliation given
Vopr Onkol; 28(1):76-83 1982

Clinical and experimental data on the carcinogenic effects of the products of nuclear fission (PNF) are reviewed. The incidence and spectrum of PNF-induced tumors depended upon the radiation dosage, the age of the animal, and the nature of PNF. Exposure to chemical carcinogens was shown to enhance the incidence of PNF-induced neoplasms. Administration of thyrostatic agents provided protection against carcinogenic effects of iodine radioisotopes. (32 Refs) (In RUS)

47. PRINCIPLES OF CANCER BIOLOGY: ETIOLOGY AND PREVENTION OF CANCER.

Upton AC
Dept. Environmental Medicine, New York Univ. Medical Center, New York, NY
Cancer - Principles and Practice of Oncology. DeVita VT, Hellman S, and Rosenberg SA, ed. Philadelphia, Lippincott, 1926 pp., 1982.

Somatic mutation, aberrant differentiation, virus activation, and cell selection form the basis of contemporary theories of carcinogenesis. None of these theories accounts for all of the observed phenomena of neoplasia. Both initiating and promoting factors seem to be required for chemical carcinogenesis in humans. The development of sound safety standards and codes of practice are the best means of risk avoidance, but the development of these standards has often lagged behind the demonstration of carcinogenicity. The problems has been complicated by uncertainty and controversy about the criteria for the determination of the carcinogenicity of a given agent, and also for assessing the magnitude of the risk occurring in exposed populations. Workable interim approaches to the resolution of these problems have been developed. (194 Refs)

48. CARCINOGENESIS AND CURRENT HYPOTHESIS ON THE TUMOR-HOST INTERACTIONS.

Neiman IM
No affiliation given
Patol Fiziol Eksp Ter; (2):63-70 1981

Current theories of cancer etiology are reviewed with special emphasis on the role of tumor-host interactions and genetic

predisposition of the host. It was suggested that exogenous factors (chronic inflammations, chemical and physical carcinogens, oncogenic viruses) can induce the precancerous conditions. Cancer development requires specific malignant transformation, which can take place only in tissues with genetic predisposition. (27 Refs) (In RUS)

49. THE ROLE OF URINE IN A PATIENT WITH A BLADDER NEOPLASM.

Melicow MM

Dept. Uropathology Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY

J Urol; 127(4):660-664 1982

A review was done on reported cases of spontaneous regression of superficial bladder tumors in which cystectomy was preceded by bilateral ureterosigmoidostomy (the interval ranging from 21 days to 6 mo). In every case in which the tumors were superficial complete disappearance of the papillary masses was observed by the naked eye and by microscopic examination. Tumor cells persisted in those cases in which the bladder wall was involved. I propose that the urine of the patient acts as a promoter to hyperplasia and neoplasia on foci of defective urothelial cells whose special coding apparatuses had been injured or destroyed by a carcinogen. The latter need no longer be present nor need there be exposure to co-carcinogen(s), such as is associated with excess alcohol intake or cigarette smoke inhalation. Tumor cells that were found in the excised bladder wall were cells that had become invasive (cancerous) and were no longer dependent. (Author abstract) (22 Refs)

50. EVALUATION OF THE CARCINOGENIC POTENTIAL OF 2,4-DINITROFLUOROBENZENE AND ITS IMPLICATIONS REGARDING MUTAGENICITY TESTING.

Warren ST, Dolittle DJ, Chang CC, Goodman JI, Trosko JE
Center for Genetics, Univ. Illinois at the Medical Center, Sch. Basic Medical Sciences, 808 S. Wood St., Chicago, IL, 60612

Carcinogenesis; 3(2):139-145 1982

Tumor promoters are compounds which dramatically enhance the appearance of tumors when chronically applied after an initiating dose of a carcinogen. Initiators are generally considered mutagens while promoters have previously been shown not to induce either DNA damage or mutations. 2,4-Dinitrofluorobenzene (2,4-DNFB), a compound used in the identification of N-terminal amino acids of polypeptides, has been previously reported to be a tumor promoter in mouse skin, while other investigators have found it to be a mutagen in bacteria and yeast. To investigate this apparent discrepancy, we chose to study the carcinogenic potential of 2,4-DNFB utilizing various methods available in V79 Chinese hamster cells. 2,4-DNFB exposure did not result in any unscheduled DNA synthesis, a measure of DNA excision repair, nor did it increase the frequency of sister chromatid exchanges in V79 cells either in the presence or absence of rat liver postmitochondrial supernatant (S-15). Forward mutations in V79 cells, either to ouabain or 6-thioguanine resistance, were not induced by 2,4-DNFB, in the presence or absence of S-15, 2,4-DNFB was, however, able to induce reversions in methionine-requiring E coli auxotrophs in a dose-dependent fashion. Phylogenetic differences between lower organisms and mammals may account for this discordance. 2,4-DNFB was found to inhibit metabolic cooperation, in a dose dependent manner, in V79 cells. This property has previously been shown to be correlated with tumor promoting ability in mouse skin. Therefore, we conclude that the carcinogenic potential of 2,4-DNFB might reside in its ability as a tumor promoter and not as a carcinogenic initiator. Furthermore, these studies serve to illustrate the need for caution when extrapolating bacterial data for risk assessment in humans. (Author abstract) (42 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. TOXICITY AND METABOLISM OF ACRYLONITRILE.
Sapota A, Chmielnicka J
Zaklad Metabolizmu Substancji Toksycznych, Instytut Medycyny Pracy, ul. Teresy 8, 90-950 Lodz, Poland
Med Pr; 32(1):25-33 1981
In POL

2. A REVIEW OF THE GENOTOXICITY OF FOOD, DRUG AND COSMETIC COLOURS AND OTHER AZO, TRIPHENYLMETHANE AND XANTHENE DYES.
Combes RD, Haveland-Smith RB
Dept. Biological Sciences, Portsmouth Polytechnic, King Henry I St., Portsmouth, PO1 2DY, Hants, England
Mutat Res; 98(2):101-248 1982

3. CARCINOGENICITY OF AIRBORNE FINE PARTICULATE BENZO(A)PYRENE: AN APPRAISAL OF THE EVIDENCE AND THE NEED FOR CONTROL.
Perera F
Natl. Resources Defense Council, Inc., 122 East 42nd St., New York, NY, 10168
Environ Health Perspect; 42:163-185 1981

4. TOXICOLOGY OF N-NITROSO COMPOUNDS.
Coulston F, Olajos EJ
Albany Medical Coll., Albany, NY, 12208
Ecotoxicol Environ Saf; 6(1):89-96 1982

5. CRITICAL REVIEW OF THE MUTAGENIC AND OTHER GENOTOXIC EFFECTS OF DIRECT COAL LIQUEFACTION.
Kimball RF, Munro NB
Oak Ridge Natl. Lab., Oak Ridge, TN
Critical Review of the Mutagenic and Other Genotoxic Effects of Direct Coal Liquefaction. Available from National Technical Information Service, Springfield, VA, as DE81027859:, 216 pp., 1981.

6. CARCINOGENICITY AND ITS EFFECT ON MEDICINAL RESEARCH PROGRAMS IN THE USA.
Van Ryzin RJ
Pharmaceutical Res. and Development, Sandoz, Inc., East Hanover, NJ, 07936
Med Res Rev; 2(2):153-166 1982

7. ANTIPROTOZOAL DRUGS (SIDE EFFECTS).
Nir I
Dept. Pharmacology and Experimental Therapeutics, The Hebrew Univ., Hadassah Medical Sch., Jerusalem, Israel
Side Eff Drugs Annu; (5):278-284 1981

8. DRUGS USED IN TUBERCULOSIS AND LEPROSY (SIDE EFFECTS).
Elis J
Inst. Pharmacology, Czechoslovak Acad. Sciences, Albertov 4, Prague 2, Czechoslovakia
Side Eff Drugs Annu; (5):290-297 1981

9. SEX HORMONES AND RELATED COMPOUNDS, INCLUDING ORAL CONTRACEPTIVES.
Plotz EJ, Nocke W, Schander K, Patt V, Kaulhausen H
Dept. Obstetrics and Gynecology, Univ. Bonn, 5300 Bonn-Venusberg, W. Germany
Side Eff Drug Annu; (5):358-380 1981

RADIATION CARCINOGENESIS

10. NEPTUNIUM - THE NEGLECTED ACTINIDE: A REVIEW OF THE BIOLOGICAL AND ENVIRONMENTAL LITERATURE.
Thompson RC
Biology Dept., Pacific Northwest Lab., Richland, WA, 99352
Radiat Res; 90(1):1-32 1982

11. CARCINOGENIC EFFECT OF RADIOACTIVE PRODUCTS.
Vasilenko IIa
No affiliation given
Vopr Onkol; 28(1):76-83 1982
In RUS

DIETARY FACTORS IN CARCINOGENESIS

12. FIBRES, NUTRITION AND THE GUT.
Schrijver M, Tytgat GN
Dept. Internal Medicine, Div. Gastroenterology, Univ. Amsterdam, 1 e Helmerstraat 104, 1054 EG Amsterdam, The Netherlands
Neth J Med; 25(2):49-55 1982

13. DIETARY FIBER AND DISEASE.
Kritchevsky D
Wistar Inst. Anatomy and Biology, Philadelphia, PA
Bull NY Acad Med; 58(3):230-241 1982

14. ASSESSING HUMAN EPIDEMIOLOGIC DATA ON DIET AS AN ETIOLOGIC FACTOR IN CANCER DEVELOPMENT.
Enstrom JE
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Bull NY Acad Med; 58(3):313-322 1982

15. NUTRITION AND CANCER: MECHANISMS OF GENOTOXIC AND EPIGENETIC CARCINOGENS IN NUTRITIONAL CARCINOGENESIS.
Weisburger JH, Horn C
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16. THE AH LOCUS, A MULTIGENE FAMILY NECESSARY FOR SURVIVAL IN A CHEMICALLY ADVERSE ENVIRONMENT: COMPARISON WITH THE IMMUNE SYSTEM.
Nebert DW
Developmental Pharmacology Branch, National Inst. Child Health, NIH, Bethesda, MD, 20205
Adv Genet; 21:1-52 1982

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

17. SKIN CANCER: OCCUPATIONAL CAUSES.
Hickers DR
Dept. Dermatology, Case Western Reserve Univ., Cleveland, OH
Consultant; 22(4):392-393,397,400-401 1982

18. OCCUPATIONAL AND ENVIRONMENTAL HEALTH PROBLEMS OF THE DEVELOPING OIL SHALE INDUSTRY: A REVIEW.
Rom WN, Lee JS, Craft BF
Rocky Mountain Center Occupational and Environmental Health, Dept. Internal Medicine, Family and Community Medicine, Univ. Utah Sch. Medicine, Bldg. 512, Salt Lake City, UT, 84112
Am J Industr Med; 2(3):247-260 1981

19. POLYCYCLIC AROMATIC HYDROCARBONS IN THE OCCUPATIONAL ENVIRONMENT: WITH SPECIAL REFERENCE TO BENZO[A]PYRENE MEASUREMENTS IN SWEDISH INDUSTRY.
Lindstedt G, Sollenberg J
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Scand J Work Environ Health; 8(1):1-19 1982

20. GENETIC RISKS AND ENVIRONMENTAL SURVEILLANCE: EPIDEMIOLOGICAL ASPECTS OF MONITORING INDUSTRIAL POPULATIONS FOR ENVIRONMENTAL MUTAGENS.
Buffler PA, Aase JM
Sch. Public Health, Univ. Texas Health Science Center at Houston, P.O. Box 20186, Houston, TX, 77025
JOM; 24(4):305-314 1982

21. OSHA AT THE THRESHOLD: SETTING PERMISSIBLE EXPOSURE LEVELS FOR KNOWN CARCINOGENS AFTER AMERICAN PETROLEUM INSTITUTE.
Blackmar GB
No affiliation given
San Diego Law Rev; 18(4/5):633-661 1981

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23. MODIFICATIONS OF CHROMATIN STRUCTURE IN CONTROL OF GENE EXPRESSION.
Hull LA
104 Depot St., New Sharon, IA, 50207
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24. PLASMINOGEN ACTIVATORS IN NEOPLASTIC CELLS.
Goloborod'ko OP, Veremeenko KN
A. I. Kolomiichenko Res. Inst. Otolaryngology, Kiev, USSR
Eksp Onkol; 4(1):3-7 1982
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25. TUMOR PROMOTION BY REGENERATIVE EPIDERMAL HYPERPLASIA IN MOUSE SKIN.
Argyris TS
Dept. Pathology, Upstate Medical Center, State Univ. New York, Syracuse, NY, 13210
J Cutan Pathol; 9(1):1-18 1982

26. SEX HORMONES AND LIVER CANCER.
Williams GM
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27. UTILIZATION OF CELL TRANSFORMATION TESTS IN THE DETECTION OF CHEMICAL CARCINOGENS.
Elias Z, Cavelier C
Institut National de Recherche, Centre de Recherche de Nancy, avenue de Bourgogne, F-54500 Vandoeuvre-les-Nancy, France
Bull Cancer (Paris); 69(1):33-57 1982
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Health Phys; 42(3):267-284 1982

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29. CANCER. AN INTRODUCTION.
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Cancer. An Introduction. New York, Oxford University Press, 271 pp., 1981.

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Cancer; 49(9):1739-1745 1982

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MODIFICATION OF CARCINOGENESIS

SERIES CK04 No. 82/10 OCTOBER, 1982

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MODIFICATION OF CARCINOGENESIS BY CHEMICAL AGENTS OR IRRADIATION

1. PROMOTING EFFECTS OF 3-AMINO-1,2,4-TRIAZOLE ON THE DEVELOPMENT OF THYROID TUMORS IN RATS TREATED WITH N-BIS(2-HYDROXYPROPYL)NITROSAMINE.

Hiasa Y, Ohshima M, Kitahori Y, Yuasa T, Fujita T, Iwata C
First Dept. Pathology, Nara Medical Univ., Kashihara, Nara, 634, Japan
Carcinogenesis; 3(4):381-384 1982

3-Amino-1,2,4-triazole (AT) promoted the development of thyroid tumors in rats treated with a subeffective dose of N-

HE 20.3173/2:

bis(2-hydroxypropyl)nitrosamine (DHPN) for thyroid tumorigenesis. The incidences of thyroid tumors at the end of the 20-wk experiment were 91% in rats injected sc once a wk for 4 wk with 70 mg DHPN per 100 g body wt and then given diet containing 2,000 ppm AT for 12 wk, 100% in rats injected sc once a wk for 8 wk with 70 mg DHPN per 100 g body wt and then given diet containing 2,000 ppm AT for 12 wk, and 58% in rats injected sc once a wk for 8 wk with 70 mg DHPN per 100 g body wt. Rats only injected sc once a wk for 4 wk with DHPN or only given diet containing AT for 12 wk had no thyroid tumors at the end of the experiment. (Author abstract) (28 Refs)

2. AN EVALUATION OF DIMETHYLNITROSAMINE (DMN) - INDUCED HEPATOCELLULAR ALTERATIONS IN THE NEWBORN MOUSE MODEL USING HISTOCHEMICAL AND HISTOENZYMATIC MARKERS (MEETING ABSTRACT)

Cater KC, Gandolfi AJ, Sipes IG
Toxicology Program, University of Arizona, Tucson, AZ, 85724
Toxicologist; 2(1):99 1982

Newborn Swiss mice were dosed IP with 25 ug of DMN or saline, and at weaning placed on drinking water containing 0.05% phenobarbital (PB), a known promoter of hepatocellular carcinomas, or water alone, Preneoplastic foci (F) and hyperplastic nodules (HN) were identified histologically by two markers; resistance to exogenous iron accumulation and an increase in gamma-glutamyl transpeptidase (GGT) activity. F were distinguished from HN by size and by compression of the surrounding parenchymal cells. In the DMN and PB group, livers of affected male mice at 6,8,12 and 16 wk exhibited 6,10,17 and 12 iron resistant F/cm2 and 10,13,9 and 9 GGT-F/cm2, respectively. At these same time periods iron resistant-F in affected females ranged from 5-11 F/cm2, while GGT-F ranged from 9-16 F/cm2. Iron resistant HN were first observed in male mice at 8 wk; however, GGT-HN were not noted until 12 wk. By 12 and 16 wk affected males had 6 and 4 iron resistant HN/cm2 while affected females had 4 and 6, respectively. At these same time points, males had 6 and 3 GGT-HN/cm2 while females only displayed GGT-HN at 16 wk (6 HN/cm(2)). The DMN alone group contained an average of 4 F/cm2 (iron resistant or GGT) while no HN were noted in any group except the DMN and PB. Lung nodules were apparent as early as 6 wk in both sexes of the DMN alone group and at 12 wk in the DMN and PB group. (no Refs)

3. COCARCINOGENICITY OF SACCHARIN TOWARD N-DIBUTYL-NITROSAMINE CARCINOGENICITY IN RAT LIVER AND URINARY BLADDER (MEETING ABSTRACT)

Pereira MA, Britz AL
Health Effects Research Laboratory, US Environmental Protection Agency, Cincinnati, OH
Toxicologist; 2(1):64 1982

Saccharin has been demonstrated to be a promoter of chemical carcinogenesis in the rat urinary bladder. Since other tumor promoters are also cocarcinogens, we evaluated the possibility that saccharin is also a cocarcinogen. Male Fisher 344 rats simultaneously received 0.02% dibutylnitrosamine (DBN) in their drinking water and 5% sodium saccharin in their diet for a total of 26 weeks. The liver of rats that received only DBN contained 16 hyperplastic nodules among 5 of 29 (17%) animals and 2 hepatocellular carcinomas in 1 of 29 (3%) of the animals. The simultaneous administration of sodium saccharin to the animals that received DBN, produced an enhanced hepatocarcinogenic response of 106 hyperplastic nodules in 17 of 21 (81%) animals and 81 hepatocellular carcinomas in 17 of 21 (81%) animals. The number of preneoplastic focal alterations in the liver that were induced by DBN, was also enhanced by sodium saccharin. The livers of untreated control rats an rats that received only sodium saccharin were free of preneoplastic foci, hyperplastic nodules and hepatocellular carcinomas. In the urinary bladder, treatment with DBN produced simple and nodule hyperplasia that was enhanced by simultaneous treatment with saccharin. Sodium saccharin did not result in either a preneoplastic hyperplasia or a neoplastic response in the urinary bladder of the rats. (no Refs)

4. EFFECT OF MOLYBDENUM ON N-NITROSOSARCOSINE ETHYL ESTER-INDUCED CARCINOGENESIS IN RATS (MEETING ABSTRACT)

Wei HJ, Luo XM, Sproat HF, Yang SP
Department of Chemical Etiology and Carcinogenesis, Cancer Institute, Beijing, China
Fed Proc; 41(3):280 1982

Male weanling rats of the Sprague-Dawley strain were given ad libitum for 19 or 30 weeks a nutritionally adequate diet and deionized drinking water (Groups 1 and 4) or the same diet and 100 ppm Mo from Na(2)Mo0(4) (Groups 2 and 5) or 20 ppm Mo (Groups 3 and 6) or 2 ppm Mo (Group 7) from Na2Mo0(4) added to the drinking water. As determined by a catalytic polargraphic procedure, the diet contained 0.026 ppm Mo and no detectable Mo in the drinking water. Starting from the third week, all the animals in Groups 4-7 were administered via gastric intubation 0.7 g sarcosine ethyl ester and 0.3 g NaN0(2) in 10 ml 0.01 N HCl per kg of body weight twice weekly for 8 consecutive weeks. N-nitrososarcosine ethyl ester (NSEE) is believed to be formed readily under the above condition. At the end of 19 weeks, 80% of the animals in Group 4 developed esophageal and forestomach cancer. This incidence was identical to that of Group 5 and significantly higher than that of Group 6 or Group 7. Similar results were obtained at the end of 30 weeks. No carcinomas were observed in Groups 1-3. (no Refs)

5. INDUCTION OF HYPERPLASTIC LIVER NODULES IN HEPATECTOMIZED RATS TREATED WITH 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE, BENZO[A]PYRENE OR PHENOBARBITAL BEFORE OR AFTER EXPOSURE TO N-2-FLUORENYLACETAMIDE.

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Gan; 73(2):264-269 1982

The effects of pre- and post-administration of 3'-methyl-4-dimethylaminoazobenzene (3'-Me-DAB), benzo[a]pyrene (B[a]P), and phenobarbital (PB) on the induction of hyperplastic liver nodules by N-2-fluorenylacetamide (2-FAA) were studied in F344 rats. Rats were given 3'-Me-DAB (0.06% in the diet), B[a]P (80 mg/kg b wt x 7, intragastrically) or PB (0.05% in the diet) for 6 wk before (experimental series I) or after (experimental series II) diet containing 0.02% 2-FAA for 2 wk, and killed in wk 10 of the experiment. The number and total area of hyperplastic nodules per unit area of liver were greatest in rats treated with 3'-Me-DAB in both experimental series. B[a]P significantly increased the induction of hyperplastic nodules in experimental series I and PB significantly increased it in experimental series II. Partial hepatectomy performed during administration of test chemicals enhanced the induction of hyperplastic nodules, especially in experimental

series I and an oral dose of carbon tetrachloride during 2-FAA feeding enhanced it in both experimental series. In the present system, initiating activity of both the hepato- and the non-hepatocarcinogen was detected, and promoting activity of both the hepatocarcinogen and the hepatopromoter was demonstrated. (Author abstract) (23 Refs)

6. ASSESSMENT OF THE CAPACITY OF 3,3',4,4',5,5'-HEXABROMOBIPHENYL TO SERVE AS A PROMOTER OF HEPATOCARCINOGENESIS (MEETING ABSTRACT)

Jensen RK, Sleight SD, Goodman JI, Millis CD, Aust SD, Trosko JE
Department of Pathology, Michigan State University, East Lansing, MI, 48824
Toxicologist; 2(1):99 1982

The objective of this study was to determine if 3,3',4,4',5,5'-hexabromobiphenyl (HBB) can act as a promoter of hepatocarcinogenesis. This congener and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) are similar in that they both cause 3-methylcholanthrene type induction of hepatic microsomal drug-metabolizing enzymes and produce a similar and characteristic pattern of toxic and histologic responses. TCDD has been shown to be a promoter of hepatic cancer in rats. To test the tumor promoting capacity of HBB, female Sprague-Dawley rats weighing 200-250 g were injected ip with diethylnitrosamine (DEN) at a dose of 10 mg/kg 24 hours after a 2/3 partial hepatectomy (PH). Thirty days after PH, groups of 6 rats were fed control diets or diets containing 1 ppm HBB or 500 ppm phenobarbital (Pb). Groups of 3 rats without prior hepatectomy or DEN were fed the same diets. At 6 months, rats were killed and samples were collected for histologic and histochemical evaluation. Gamma glutamyl transpeptidase (GGT) was used to identify enzyme altered foci. The average number of GGT positive foci/cm2 were: control, 0; Pb, 58; HBB, 79. Values for rats not hepatectomized or given DEN were: control, 0; HBB, 11. Rats fed HBB had decreased weight gain and thymic atrophy. Histologically, the liver had severe hepatocellular swelling and vacuolation and focal areas of necrosis. (no Refs)

MODIFICATION OF CARCINOGENESIS BY DIETARY COMPONENTS OR DIGESTIVE FACTORS

7. INHIBITION OF THE HEPATOCARCINOGENIC ACTIVITY OF DIETHYLNITROSAMINE (DENA) BY ETHANOL IN RATS.

Habs M, Schmahl D
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Hepatogastroenterology; 28(5):242-244 1981

Male Sprague-Dawley rats received 0.1 mg/kg of diethylnitrosamine orally 5 times a wk for life with or without additional subsequent administration of 5 ml/rat/day of a 25% aqueous solution of ethanol. The additional treatment with ethanol significantly reduced the induction of liver cancer, but not of esophageal tumors. These findings do not support speculations based on epidemiologic studies as to a cancer-causing effect of alcohol. (Author abstract) (11 Refs)

8. INHIBITION OF PANCREATIC CARCINOGENESIS BY RETINOIDS IN AZASERINE TREATED RATS (MEETING ABSTRACT)

Longnecker DS, Kuhlmann ET, Curphey TJ
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Fed Proc; 41(3):683 1982

Chemoprevention by retinoids of the progression of azaserine-induced carcinomas and preneoplastic lesions in rats was evaluated. Lewis rats were given 5 weekly injections of 30 mg/kg of azaserine while fed a chow diet, and then were fed chow supplemented with retinoids at the level of 0.5-2.0 mmol/kg diet for 1 year. The incidence of neoplasms was determined by autopsy and histologic study. The incidence of localized pancreatic carcinomas among a male positive control group (azaserine-treated, but not retinoid-treated) was 24% and in female group was 17%. The incidence of pancreatic carcinomas among male and female groups treated with N-4-pivaloyloxyphenyl retinamide was 4% and 0%, respectively. These were significantly below the control group incidence. Animals fed N-2-hydroxypropyl retinamide, N-3-hydroxypropyl retinamide (3HPR) and N-2,3-dihydroxypropyl retinamide (2,3HPR) showed a similar trend in both sexes but significance was reached only in the female groups fed the 3 HPR and 2,3HPR. Since retinoids were fed after exposure to carcinogen, the effect was exerted during the postinitiation phase of carcinogenesis. The ratio of localized and early invasive carcinomas to earlier precursor lesions was clearly higher among non-retinoid treated rats than among those treated with retinoids. This is consistent with an inhibition of progression in the retinoid-treated groups. (no Refs)

9. PREVENTION OF THE BENZO(ALPHA)PYRENE PHOTOCARCINOGENIC EFFECT BY B-CAROTENE AND CANTHAXANTHINE (MEETING ABSTRACT)

Santamaria L, Bianchi A, Arnaboldi A, Andreoni L
University of Pavia, Pavia, Italy
Med Biol Environ; 9(1):113 1981

Beta-carotene (C) and canthaxanthine (CX) were perorally administered to female Swiss albino mice, with daily diet. One month after initiating the above dietary treatment, the mice were given additional administrations of C and CX by catheter twice a week. They were then painted with benzopyrene (BP) and were either exposed to long UV light (300-400 nm with maximum output at 365 nm) twice a week or kept in the dark. Tumors appeared earlier and grew more rapidly in BP-painted and long UV irradiated mice; thus, confirming the 'BP photocarcinogenic effect'. C and CX substantially prevented such an effect (respectively, 79% and 66%, as compared to carcinogenesis in the dark), demonstrating the relevance of carotenoids in the development of rational programs of skin cancer prevention in occupational medicine. (no Refs)

10. PROTECTIVE EFFECT OF NICOTINAMIDE ON BRACKEN FERN INDUCED CARCINOGENICITY IN RATS.

Pamukcu AM, Milli U, Bryan GT
Div. Clinical Oncology, Dept. Human Oncology, Wisconsin Clinical Cancer Center, K4/554, CSC, 600 Highland Ave., Madison, WI, 53792
Nutr Cancer; 3(2):86-93 1981

Albino noninbred weanling male and female rats were fed a basic grain diet (Group 1), a basic diet supplemented with 0.5% nicotinamide (Group 2), a basic diet containing 33%

bracken fern (BF) (Group 3), or a basic diet supplemented with 33% BF and 0.5% nicotinamide (Group 4) for 58 wk. Dietary nicotinamide decreased the BF-induced incidence of both intestinal and bladder tumorigenesis by about 40%. The inhibitory effect of nicotinamide on the BF-induced intestinal and bladder tumors was significant at p less than 0.05 and p less than 0.01, respectively. (Author abstract) (39 Refs)

11. DIFFERENTIAL EFFECTS OF DIETARY ANTIOXIDANTS ON CHEMICAL CARCINOGENESIS (MEETING ABSTRACT)

King MM, McCay PB
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Fed Proc; 41(3):358 1982

Female weanling Sprague-Dawley rats were fed a defined semipurified diet with antioxidants being supplemented throughout the experiments as indicated. In one set of experiments, the diets were supplemented with butylated hydroxytoluene (BHT). The rats were given a 10 mg oral dose of 7,12-dimethylbenz(a)anthracene at 50 days of age. The incidence of mammary adenocarcinomas was markedly lower in the BHT-supplemented rats compared to rats fed the same diet without BHT. When butylated hydroxyanisole (BHA) was supplemented in the diet instead of BHT, no inhibition of mammary tumor development was observed. In similar experiments, it was found that propyl gallate supplementation also offers protection against DMBA-induced tumorigenesis while alpha-tocopherol does not. These results raise the question: is the antioxidant property of the supplement actually related to inhibition of tumorigenesis or is it some other property of particular antioxidants (in this case, BHT and propyl gallate)? To determine if BHT may possibly be affecting some metabolic system associated with the activation of DMBA to the ultimate carcinogen, the effect of BHT supplementation on tumor induction was compared between a direct acting mammary carcinogen (nitrosomethylurea) and DMBA, which does require metabolic activation. BHT inhibited DMBA- but not NMU-induced mammary tumorigenesis, suggesting that the influence of BHT may involve inhibition of DMBA activation. (no Refs)

12. CAFFEINE AND UNSATURATED FAT DIET SIGNIFICANTLY PROMOTES DMBA-INDUCED BREAST CANCER (MEETING ABSTRACT)

Minton JP, Foecking MK, Abou-Issa H
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Joint Meeting of the Society of Surgical Oncology and Society of Head and Neck Surgeons, April 18-23, 1982, Marco Island, Florida. The Society of Surgical Oncology and the Society of Head and Neck Surgeons 265 pp., 1982.

Caffeine is an important causative agent in the development of human fibrocystic breast and disease. The epithelial proliferation resulting from caffeine consumption has been shown to be reversible when caffeine abstention is carried out. The exposure of a well-established animal model to the known carcinogen dimethylbenz(a)anthracene (DMBA) is associated with the development of a hormone sensitive estrogen receptor positive breast tumor in nearly 90% of the animals. To determine the possibility of caffeine being an extraordinary promoter of breast cancer development in animals consuming vegetable fat the following study was carried out. A controlled study comparing the time to tumor development and the number of tumors and the growth rate of breast cancer in Sprague-Dawley rats which had been given 50 mg of DMBA at 6 weeks of age compared the tumor promotional effects of caffeine alone, caffeine and unsaturated fatty acids in combination, unsaturated fatty acids alone, and a standard rat chow diet. Twenty rats were in each group. The results show that the rat which consumed caffeine and unsaturated fatty acids had the earliest development of tumor, the most multiple tumor occurrence, and the most rapid rate of growth. Average time to development was 94 days. The fat and water rats had an average time of development of 133 and 140 days respectively. The caffeine alone rats had a mean time to tumor development of 188 days. The combination of an unsaturated fat diet and caffeine significantly shortened the time to tumor development when compared with the other three groups. (no Refs)

13. THE ACUTE EFFECT OF BETA-SITOSTEROL ON COLONIC EPITHELIAL CELL PROLIFERATION: IMPLICATIONS FOR MNU-INDUCED NEOPLASIA (MEETING ABSTRACT)

Deschner EE, Cohen BI, Raicht RF
Memorial Sloan-Kettering Cancer Center, New York, NY
Cell Tissue Kinet; 15(1):102 1982

The effect of dietary supplementation with beta-sitosterol (0.2% of diet) was followed in Fisher rats after a period of 3 and 7 days feeding. Compared with controls, the number of epithelial cells per crypt column in both plant sterol fed groups was shifted to lower values; moreover, fewer epithelial cells above cell position 12 were engaged in DNA synthesis. Rats treated with MNU (methylnitrosourea) intrarectally (2 mg) while consuming beta-sitosterol demonstrated a reduction in the number of [3H]TdR (thymidine) labelled cells per crypt column from that seen in rodents receiving just the carcinogen. Twenty-six weeks later, MNU-treated rats fed beta-sitosterol showed a significantly decreased colonic tumor incidence (1.3 tumor per tumor-bearing animal vs 2.1 tumor per tumor-bearing animal). This plant sterol which passes through the digestive tract relatively unabsorbed appears to slow colonic epithelial cell proliferation resulting in a reduced expression of neoplastic transformation. (1 Ref)

MODIFICATION OF CARCINOGENESIS BY HORMONAL OR GENETIC FACTORS

14. DIMETHYLHYDRAZINE-INDUCED COLONIC NEOPLASIA: DISSOCIATION FROM ENDOGENOUS GASTRIN LEVELS.

Oscarson JE, Veen HF, Ross JS, Malt RA
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Surgery; 91(5):525-530 1982

The potential tropic effect of gastrin in promoting colonic carcinogenesis was tested in rats (n = 133) with 6-to 16-fold variations in endogenous gastrin resulting from antrectomy or fundectomy, followed by 12 injections of 1,2-dimethylhydrazine (10 mg/kg). The incidence and grade of differentiation of resulting tumors, as well as the thickness, content of nucleic acids, and specific activity of DNA in colonic mucosa, were similar in both high-gastrin and low-gastrin animals and were unchanged from data in unoperated control animals receiving only the carcinogen. Long-term changes in endogenous gastrin concentration are not followed by colonic mucosal tropic effects, and gastrin does not act as a cofactor in dimethylhydrazine-induced carcinogenesis at this dosage. (Author abstract) (25 Refs)

15. CHOLECYSTOKININ INHIBITS NITROSAMINE-INDUCED CARCINOGENESIS (MEETING ABSTRACT)

Johnson FE, LaRegina MC, Martin SA, Bashiti HM
St. Louis University Medical Center, St. Louis, MO
Joint Meeting of the Society of Surgical Oncology and Society of Head and Neck Surgeons, April 18-23, 1982, Marco Island, Florida. The Society of Surgical Oncology and the Society of Head and Neck Surgeons 265 pp., 1982.

Acute administration of cholecystokinin (CCK) has well-known effects on gall bladder contractions and pancreatic-biliary secretion. Recent data indicates that chronic administration of CCK has trophic effects on abdominal viscera, particularly pancreas. In order to determine whether CCK enhances malignant growth as well as growth of normal organs, we administered CCK together with di-isopropanol nitrosamine (DIPN), a carcinogen known to induce pancreatic, hepatic (and other) carcinomas. Two hundred young male Syrian golden hamsters (approx 60 gm) were divided into four groups. Group A (80 animals received DIPN (250 mg/kg) plus CCK (20 U/kg) by weekly subcutaneous injections; Group B (80 animals), DIPN alone; Group C (20 animals), CCK alone; Group D (20 animals), saline. Injections were done for 40 weeks, with animal sacrifice and autopsy at 10, 14, 18, 27, and 40 weeks. Microscopic study of pancreas, liver, heart, lung, brain, spleen small intestine, large intestine, testis, kidney, and stomach was carried out in each animal. Animal weights and visceral weights showed no striking differences between groups. Microscopic examination of the pancreas showed: DIPN induced pancreatic and hepatic carcinomas; CCK administration appeared to prevent their development. The mechanism of this effect is unknown. These results have implications for human carcinogenesis, and some of the implications are testable by currently available methods. (no Refs)

16. EFFECTS OF MEDROXPROGESTERONE ACETATE ON THE DEVELOPMENT OF DIMETHYLBENZANTHRACENE-INDUCED MAMMARY TUMORS. POSSIBLE MODES OF ACTION (MEETING ABSTRACT)

Danguy A, Legros N, Leclerq G, Heuson JC
Laboratory of Histology and Laboratory of Mammary Oncology, Brussels, Belgium
International Symposium on Medroxyprogesterone Acetate, February 24-26, 1982, Geneva, Switzerland. Farmatalia Carlo Erba 91 pp., 1982.

Our purpose was to describe the effects of different doses of Medroxyprogesterone acetate (MPA) on growth of 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary tumors and to study the underlying endocrine mechanisms. This experimental model is extensively studied in order to understand the hormonal dependency of human breast cancer. MPA was administered sc at doses of 1 mg/kg, 10 mg/kg and 100 mg/kg 6 days a week for 6 weeks. The smaller dose enhanced tumor growth whereas the higher one was significantly inhibitory. The administration of 100 mg/kg/day of the drug to ovariectomized rats significantly inhibited the increase in body weight as compared to ovariectomy alone. In the animals treated with 10 and 100 mg/kg/day the ovaries contained very small follicles and no corpora lutea; the adrenals were also distinctly small with atrophy of the cortical components. Using sensitive histological (Peroxidase anti-Peroxidase Complex unlabelled antibody stain, immunofluorescence) and endocrine (Radioimmunoassay) techniques we were able to demonstrate the modifications produced by MPA in the pituitary gland and the serum: atrophy of adenocorticotropes, gonadotropes and mammotropes as well as decrease in plasma Luteinizing Hormone (LH) and Prolactin (PRL). So the antitumor activity of MPA may be explained by a partial pharmacological hypophysectomy. However it remains possible that part of the inhibitory action of MPA may be exerted directly at the tumor level. Indeed, the action of MPA via the progesterone receptor and a direct cytotoxic effect of the drug must be drawn into consideration. (no Refs)

17. EFFECT OF ESTRADIOL PROPIONATE AND PREGNANCY ON CARCINOGENESIS INDUCED BY 1,2-DIMETHYLHYDRAZINE IN C3HA MICE.

Turusov VS, Murovannyi AN, Morozova OV
All-Union Cancer Res. Center, Moscow, USSR
Eksp Onkol; 4(2):20-23 1982

The effects of pregnancy and estradiol propionate (EP) administration on 1,2-dimethyl hydrazine (DMH)-induced carcinogenesis were studied in female C3HA mice. Virgin or pregnant females were subjected to sc administrations of DMH (8 mg/kg/wk) alone or in combination with EP (10 ug/kg/wk). DMH and EP were given for 30 wk. Animals were followed up for 50 wk after the initiation of the experiment. DMH alone induced tumors in 75% of virgin mice and in 56.2% of pregnant mice. EP administration resulted in a marked increase of the incidence of colonic tumors (31.6%, compared with 8.3% after administration of DMH alone to virgin mice and 18.7% after administration of DMH alone to pregnant mice). Uterine sarcomas were observed in 28.9% of mice treated with DMH + EP, while all mice treated with DMH alone were free of uterine sarcomas. Hepatocellular tumors were observed only in mice treated with DMH + EP (23.7%). These findings indicate that EP can modify the DMH-induced carcinogenesis not only in the hormone dependent organs but also in the liver and in the colon. (14 Refs) (In RUS)

18. GROWTH FACTORS (GF) AND TRANSITIONAL CELL CARCINOMA (TCC): THEIR INTERACTION EVALUATED WITH THE AID OF A SERUM-FREE DEFINED MEDIUM (MEETING ABSTRACT)

Messing EM, Fahey JL, DeKernion JB, Bubbers JE
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

For our investigations of the production of new growth factors by TCC, 647V was chosen as the most appropriate subject not only because of its ability to grow in DH-S1, but also because its growth in both serum-containing and serum-free media has demonstrated a rigid dependency upon cell density. Concentrated (Amicon Filter, 500MW cut-off) conditioned serum-free media, obtained from 647V cultures in log phase growth in DH-S1, was then added to fresh DH-S1 and was found to stimulate growth of 647V cells in a direct, dose-related fashion. When this activity was compared with that of the ubiquitous epidermal growth factor (EGF), itself a naturally occurring GF which is excreted in large quantities in a biologically active form in human urine, and which has demonstrated co-carcinogenic properties, EGF failed to stimulate the growth of 647V cells when added to growth media (DH-S1) in several concentrations. Subsequent experiments which detected and measured EGF receptors on 647V and another human TCC cell line, showed that the inability of EGF to stimulate growth of these cells was not because EGF was not bound by them. Tumors characteristically are less responsive than non-neoplas-

tic tissue to normal growth regulation. The persistance of GF production by a cell which is capable of responding to that factor by dividing may result in continuous endogenous stimulation and eventually to unrestricted growth. (no Refs)

19. SEPARATION OF HIGH MAMMARY TUMOR INCIDENCE FROM HIGH HEPATOMA INCIDENCE IN BACKCROSS MICE DURING SEGREGATION OF THE VIABLE YELLOW GENE.

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Int J Cancer; 29(5):587-590 1982

Mammary tumorigenesis in strain C3H/AvyfB female mice (approx 90% incidence) is not due to exogenous mouse mammary tumor virus (MMTV) but to genetic factors transmitted by either parent. Prominent among these genetic factors is the viable yellow (Avy) gene which may increase either the virulence of the endogenous MMTV provirus (Mtv-1) by promoting expression of the susceptibility of the mammary tissue to tumorigenesis by endogenous MMTV. Unexpectedly, the F1 hybrid females (AvyA) developed mammary tumors at a relatively low rate although hepatoma incidence remained high. Both yellow (AvyA) and agouti (AA) backcross females showed an even greater reduction in mammary tumor incidence, 7.9% and 3.8% respectively. In contrast, the high rate of spontaneous hepatoma development segregated with the Avy gene since 86-5% of the yellow (AvyA) backcross females development hepatomas by 19 mo of age, while only 25% of the agouti (AA) backcross females had liver tumors at 24.4 mo. The reduction of mammary tumor incidence in (C3H-AvyfB x C3H/Sm)F1 hybrids was unexpected since earlier studies had shown that reciprocal F1 hybrids between strains BALB/c and C3H-AvyfB continued to show a 90% mammary tumor incidence. The present result is consistent with the possibility that strain C3H/Sm possesses a heritable factor(s) which attenuates the ability of endogenous MMTV to malignantly transform mammary epithelium. (15 Refs)

20. STRAIN DIFFERENCES OF TUMORIGENIC EFFECT OF NEONATALLY ADMINISTERED N-ETHYL-N-NITROSOUREA IN RATS.

Naito M, Naito Y, Ito A
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Gan; 73(2):323-331 1982

The tumorigenicity of neonatally administered N-ethyl-N-nitrosourea (ENU) was studied in four different inbred strain rats, that is Wistar/Furth (WF), Long-Evans (LE), F1 of Wistar/Furth and Long-Evans (F1) and Fischer 344 (F344) rats. All strains developed tumors of the nervous system with high incidence (97 to approx 100%) during 6 mo of observation. The incidence of tumor of the central nervous system, including the brain (82 to approx 88%) and the spinal cord (53 to approx 76%), was high in all strains, but that of the peripheral nervous system, including the cranial nerve (21 to approx 89%) and the spinal root (13 to approx 93%), differed by strain. The peripheral nervous system of WF and F344 rats had a low susceptibility to the tumorigenic effect of ENU, but that of LE rats had a high susceptibility. Many brain tumors were induced in the temporal and frontal cortex and subcortex in all strains of rats. Spinal cord tumors were observed at all levels of the white matter of the spinal cord without any predilection site. Spinal root tumors were located in lumbosacral plexuses in WF and F344 rats, but in Le and F1 rats cervical and thoracic root tumors were also observed. Histological examination revealed that most of the brain and spinal cord tumors were oligodendroglioma, but in F344 rats about half of the brain tumors were mixed glioma. Epidermoid cysts of the lumbar spinal cord were observed only in F344 rats. Tumors of the peripheral nervous system were so-called anaplastic schwannoma. (Author abstract) (23 Refs)

MODIFICATION OF CARCINOGENESIS BY VIRUSES, BACTERIA OR IMMUNE SYSTEM COMPONENTS

21. SUPPRESSOR T LYMPHOCYTES CONTROL THE DEVELOPMENT OF PRIMARY SKIN CANCERS IN ULTRAVIOLET-IRRADIATED MICE.

Fisher MS, Kripke ML
Cancer Biology Program, NCI, Frederick Cancer Res. Facility, Frederick, MD, 21701
Science; 216(4550):1133-1134 1982

Exposure of mice to ultraviolet radiation results in the development of suppressor T lymphocytes in lymphoid organs, followed by the appearance of primary skin cancers. The presence or absence of these suppressor lymphocytes determines whether or not primary cancers will develop in the ultraviolet-irradiated skin. This demonstrates the importance of immunological regulatory pathways in carcinogenesis and provides an example of immunological surveillance. (Author abstract) (18 Refs)

22. CYTOTOXICITY AND SUPPRESSION DURING RADIATION AND RADLV-INDUCED LEUKEMOGENESIS (MEETING ABSTRACT)

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Fed Proc; 41(3):417 1982

Adult C57BL/6 mice exposed to fractionated x-irradiation or inoculated with the highly leukemogenic variant of the Radiation Leukemia Virus (A-RadLV) develop high incidence lymphatic leukemias within 3-6 months. A-RadLV-induced, but not x-ray-induced lymphomas, can elicit cytotoxic responses in vitro in lymphocytes of preimmunized syngeneic mice, a reaction that is dependent on the expression of membrane associated viral antigenicity. As soon as 5 days after A-RadLV inoculation and during the entire leukemogenic process suppressor T cells are detectable in the spleen that are capable of specifically abrogating generation of syngeneic anti-tumor cytotoxic cells in vitro. These suppressor cells are generated directly by the virus, independently of initiation of the leukemogenic process. Mice exposed to fractionated x-ray irradiation or inoculated with the low leukemogenic D-RadLV variant do not develop suppressor cells and their splenocytes can be stimulated in vitro to generate cytotoxicity towards RadLV-induced leukemias. These findings suggest that: (a) although RadLV has been isolated from radiation induced leukemias, x-ray and RadLV-induced leukemogenesis do not seem to involve a common viral etiology; (b) induction of tumor specific suppression by A-RadLV may be essential for tumor progresson; and (c) the low leukemogenic potential of D-RadLV may be attributed to its inability to trigger host's suppressor cells. (no Refs)

23. POSSIBLE ROLE OF NK CELLS IN RADIATION LEUKEMOGENESIS (MEETING ABSTRACT)

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Baylor College of Medicine, Houston, TX, 77030
Fed Proc; 41(3):316 1982

Kaplan et al demonstrated that fractionated sublethal whole body irradiation of C57BL/6 mice, resulted in development of thymic-lymphoma-leukemia, but a post-irradiation transfusion of bone marrow prevented it. To investigate a possible role of natural killer (NK) cells in radiation leukemogenesis, we studied the effect of fractionated irradiation of C57BL/6 mice on NK cell activity and development of thymic lymphoma. Groups of 4-6 week old C57BL/6 mice were exposed to 225 rads of whole body irradiation, once a week for 4 weeks. Following the last radiation exposure, one group of mice was transfused with 10(7) C57 bone marrow cells. Marrow-transfused, non-transfused and control mice were tested at weekly intervals, for spleen NK cell-lysis of YAC-1 lymphoma target cells, with or without 1 or 5 days prior intraperitoneal injection of Poly I:C or Corynebacterium parvum (CP), respectively. NK cell activity was depressed from 1 to 8 weeks post treatment in fractionally-irradiated mice but was quickly restored to control levels in bone marrow transfused mice. Both CP and Poly I:C treatment partially restored NK cell activity of mice exposed to leukemogenic irradiation. The development of thymic lymphoma is being followed. The results suggest that NK cells may play a role in the control of radiation leukemogenesis. Similar results have recently been published by Parkinson et al. (no Refs)

24. PREVENTION OF TRANSPLACENTAL CARCINOGENESIS BY THE IMMUNOLOGIC HORMONE LYMPHOTOXIN (MEETING ABSTRACT)

Ransom JH, Evans CH, DiPaolo JA
National Institute of Health, Bethesda, MD, 20205
Fed Proc; 41(3):379 1982

Development of interventive measures to control cancer would be facilitated by monitoring carcinogenesis in vivo with an in vitro assay of morphologic transformation. Syrian hamsters at the 10-11th day of gestation were injected ip with 3 mg diethylnitrosamine (DEN)/100 g. Two days later, fetuses were excised, the fetal cells dissociated and 2000 cells seeded/60 mm dish for colony formation. The frequency of morphologically transformed colonies was determined after 7 days. The mean transformation frequency per cell seeded was 1 x 10(-4) with a 3.6% efficiency of colony formation. Ip injection of an immunologic hormone preparation reduced the transformation frequency by 46%. The preparation was the diafiltered and concentrated lymphokines of phytohemagglutinin stimulated hamster peritoneal leukocytes. It contained 10,000 units of lymphotoxin but no detectable interferon. When DEN exposed cells were x-irradiated with 250 R in vitro and 9000 cells seeded/dish, an increased mean transformation frequency, corrected for x-ray toxicity, of 8.5 x 10(-4) per cell seeded was observed. The DEN + x-ray cocarcinogenic frequency of transformation was reduced 64% by ip injection of the immunologic hormone. This study indicates that immunologic hormones (eg lymphotoxin) can prevent carcinogenesis in vivo and that the in vitro quantitation of transformation provides a means for assessing passively administered and autochthonous effector mechanisms which control carcinogenesis in vivo. (no Refs)

25. CHARACTERISTICS OF HUMAN EMBRYONIC LUNG CELLS (HEL) TRANSFORMED BY RESTRICTION ENDONUCLEASE (XBA) FRAGMENTED HCMV DNA (MEETING ABSTRACT)

Boldogh I, Huang ES, Gonczol E, Vaczi L
Medical University of Debrecen, Debrecen, Hungary
VI Meeting of the European Association for Cancer Research, October 12-15, 1981, Budapest, Hungary. The European Association for Cancer Research 275 pp., 1981.

The long period before tumors are detected can be a reflection of the capacity for a latent interaction which occurs with HCMV (Human Cytomegaloviruses) under natural conditions. The mechanism in nature by which the normally cytolytic HCMV infection may become a transformation event are not known. It seems that the HCMV induced carcinogenesis may be a multistep process involving an initiator (eg HCMV) and an environmental factor (cocarcinogen). To test this hypothesis, HEL cells were transfected with restriction endonuclease (Xba) cleaved HCMV DNA. The transfection was accomplished by using the calcium phosphate technique. Nineteen and 28 days after transfection cells were treated with a tumor promoting agent 12-O-tetradecanoyl-acetate (TPA). Morphologically altered foci developed 38 +/-6 days after transfection in monolayers of TPA treated and untreated HEL cells. The isolated colonies of morphologically altered cells expressed HCMV specific nuclear antigen(s) and they were positive for HCMV nucleic acids detected by in situ hybridization. From the 47 colonies three independently isolated continuous cell lines were developed and characterized. (no Refs)

26. FURTHER STUDIES ON THE INHIBITION OF CHEMICAL CARCINOGENESIS BY CORYNEBACTERIUM PARVUM.

Woodruff M, Forbes G, Speedy G
Medical Res. Council, Clinical and Cytogenetics Unit, Western General Hosp., Edinburgh EH4 2XU, Scotland
Cancer Immunol Immunother; 12(3):259-265 1982

Effects of both single and repeated injection of Corynebacterium parvum (CP) on the incidence of fibrosarcoma in response to methylcholanthrene (MC) were studied in adult female (17-22 g) mice of strains CBA and BALB/c. The carcinogen was administered by sc or ip implantation of an MC-impregnated Millipore disc. In CBA mice, repeated iv injection of CP starting on day-4 (0.7 mg every 4 wk, or 0.35 every 2 wk) significantly delayed appearance of sarcomas after sc injection of 0.5 mg MC on day 0; repeated injection of CP starting on day 24, and a single injection of CP on day-4, 6, 20, or 28, had no significant effect. In BALB/c mice, repeated injection of CP starting on day-4 or +6 significantly delayed the appearance of sarcomas after sc injection of 0.25 mg MC, and some significant inhibition occurred even when repeated administration of CP was started on day 41. After implantation of a 5% MC-wax disc sarcomas developed in 8 of 8 untreated CBA mice but in only 13 of 21 CBA mice which received repeated iv injections of CP (0.35 mg every 2 wk starting on day-4, 6, or 20). In BALB/c mice sc implanted 0.5% MC-wax discs were extruded in 4 of 16 mice which received repeated iv injections of CP; in the remaining 12 mice sarcomas developed somewhat later than in untreated mice but the difference was not statistically significant. When MC-wax discs were implanted ip, repeated injections of CP from day-4 completely prevented the development of tumors, irrespective whether the disc was attached to the liver or elsewhere in the peritoneal cavity. Sc implantation of 0.1 mg MC discs resulted in the development of fibrosarcomas in nearly all untreated mice, and

the time for tumors to develop was independent of the pore size of the disc. The pore size did, however, affect the response to CP. With discs of 0.22 micrometer pore size the development of sarcomas appeared to be somewhat delayed by repeated injection of CP starting before disc insertion, but the difference was not quite significant at the P = 0.05 level. (12 Refs)

OTHER STUDIES OF THE MODIFICATION OF CARCINOGENESIS

27. PROMOTION OF LIVER TUMORS IN B6C3F1 MALE MICE BY PARTIAL HEPATECTOMY OR DIETARY CHOLINE DEFICIENCY (MEETING ABSTRACT)

Newberne PM, Clark AJ
Department of Nutrition and Food Science, MIT, Cambridge, MA
Toxicologist; 2(1):63 1982

Groups of male weanling B6C3F1 strain of mice were fed a control semisynthetic diet (C) or the same diet devoid of choline (CD). Some mice from each group were subjected to partial hepatectomy (HepX) after two weeks on diet. Sequential sacrifices of mice from each group revealed the following: after three months, no tumors in any mice although the CD mice had enzyme deficient and fat-free islands of proliferating hepatocytes; after six months choline deficient mice only had liver tumors; after nine months control mice, 0% tumors, C+HepX mice 20% tumors, CD mice 100% tumors and CD+HepX mice 40% tumors. Autoradiographic studies indicated that both HepX and CD increased DNA synthesis and liver cell proliferation at all periods examined. These data suggest that the liver of B6C3F1 mice is sensitive to agents or conditions which are not tumorigens themselves but which may promote tumors. (no Refs)

28. STIMULATION OF MURINE SPLENIC LYMPHOCYTES AFTER SKIN PAINTING WITH A TUMOR PROMOTER (MEETING ABSTRACT)

Schoof RA, Baxter CS
Department of Environmental Health, University of Cincinnati Medical Center, Cincinnati, OH
Toxicologist; 2(1):91 1982

The tumor promoter 12-O-tetradecanoyl-phorbol-13-acetate (TPA) synergistically enhances the response of murine lymphocytes to T-cell mitogens but has very little mitogenic activity alone in vitro. In order to examine the effects of TPA in vivo, its interaction with Staphylococcus enterotoxin A (SEA), a recently reported in vivo T-lymphocyte mitogen, was investigated. Back skin of Balb/c mice was painted with 2, 6, or 10 ug of TPA in 100 ul of acetone twice weekly for two weeks. Twenty-four hours after the last dose 20 ug of SEA was administered retro-orbitally. Forty-eight hours after the SEA injection spleen lymphocyte mitogenic activity was increased in a dose-related manner, a 60% increase occurring at the highest (10 ug) dose. However, unlike its effects on lymphocytes in vitro, skin painting with TPA stimulated mitogenesis even when no other mitogen was present. Mitogenic activity in mice treated with TPA, but not with SEA, was approximately 50% of the levels induced in acetone-treated mice by injection of SEA. One application of 6 ug of TPA was sufficient to induce a two-fold enhancement of mitogenesis within 24 hours. Peak stimulation was reached between 48 and 72 hours after dosing. When mice received two weeks of TPA treatments, the maximum stimulation reached 48 hours after the last application was more than twice the maximum level achieved after one TPA application. An 8-fold enhancement of mitogenic activity was observed at that time. (no Refs)

29. PROTECTIVE EFFECTS OF BLADDER SURFACE GLYCOSAMINOGLYCANS AGAINST CARCINOGENIC AGENTS (MEETING ABSTRACT)

Bodenstab W, Stauffer C, Schmidt JD, Parsons CL
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association Missouri. American Urological Association 254 pp., 1982.

It has been shown in animal models that the bladder surface is lined by a layer of glycosaminoglycans (GAGs) that prevents bacterial adherence and infection. The GAG layer also prevents calcium and proteins from adhering to the bladder surface. We believe that GAG layer acts as a nonspecific barrier between the transitional cells and the environment, protecting them from infection, stone formation and carcinogenesis. To determine whether the GAG layer also blocks the access of carcinogens to the transitional cells we tested the tumorigenic effects of methylnitrosourea (MNU), a complete carcinogen, in 4 groups of rabbits using an in vivo assay that we have described. Group 1 received MNU only; Group 2 underwent removal of the natural GAG layer with HCl followed by treatment with MNU; Group 3 underwent HCl removal of the GAG layer and its replacement with the synthetic analog sodium pentosanpolysulfate (SP54) followed by treatment with MNU; Group 4 received SP54 followed by MNU. All rabbits' bladders were assayed for tumors at 18, 22, 26, 30 and 34 weeks. Group 2 showed the highest incidence of tumors, approximately 55%. Approximately 25% of Group 1 rabbits, 12% of Group 3 rabbits and 6% of Group 4 rabbits developed tumors. The differences between tumor incidence in the groups receiving SP54 before MNU (Groups 3 and 4) and the group receiving MNU after HCl removal of the natural GAG layer (Group 2) were statistically significant, suggesting that SP54 prevented the increased carcinogenic effects of MNU seen in bladders whose natural GAG layer had been removed. (no Refs)

STUDIES OF TUMOR PROMOTION OR COCARCINOGENESIS IN MOUSE SKIN

30. CORRELATION BETWEEN SENSITIVITY TO TUMOR PROMOTION AND SUSTAINED EPIDERMAL HYPERPLASIA OF MICE AND RATS TREATED WITH 12-O-TETRA-DECANOYLPHORBOL-13-ACETATE.

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Carcinogenesis; 3(4):403-407 1982

The role of sustained hyperplasia in tumor promotion has been reexamined in light of our previous report that the Syrian hamster, which is insensitive to two-stage epidermal carcinogenesis initiated by 7,12-dimethylbenz[a]anthracene (DMBA) and promoted by 12-O-tetradecanoylphorbol-13-acetate (TPA), does not respond with epidermal hyperplasia after multiple treatments with the promoter. Epidermal hyperplasia of several

other species and strains of animals, which vary in their responsiveness to TPA-mediated tumor promotion, was examined after single or multiple treatments with the tumor promoter TPA. The strains examined were CD-1, C57B1, Balb/c, DBA, and F 344. A striking difference was observed in the response of the different animal species to single versus multiple exposures to the promoter. When the effects of single versus multiple doses of TPA were compared, every possible combination of responses was observed, including potentiation, adaptation, and no change. Thus, the results of a single exposure could not be used to predict the response with multiple treatments. While no correlation was observed between sensitivity to tumor promotion and hyperplasia induced by a single exposure of TPA, a good correspondence was found between sensitivity to tumor promotion and TPA induced sustained hyperplasia after 4 wk of treatment. The role of sustained hyperplasia in tumor promotion and the necessity to study persistent effects induced by TPA are discussed. (23 Refs)

31. EPIDERMAL-DERMAL JUNCTION DURING EXPERIMENTAL SKIN CARCINOGENESIS AND COCARCINOGENESIS AS REVEALED BY SCANNING ELECTRON MICROSCOPY.

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J Invest Dermatol; 78(5):395-401 1982

During epidermal carcinogenesis important changes in the epidermal-dermal junction take place. Because of the methodological difficulti many of these changes, especially those concerned with three-dimensional organization of the junction, remain unsatisfactorily investigated. To obtain new information, we studied with scanning electron microscopy (SEM) the development of carcinogenic changes in the epidermis of mice induced by DMBA-TPA, (9,10-dimethyl 1,2 benzanthracene-12-O-tetra-decanoyl-phorbol-13-acetate) DMBA alone, and by the cocarcinogen TPA alone. We correlated the results with those from transmission electron microscopy and light microscopy. Although the epidermal changes morphologically showed similarities, biologically they differed. With them, distinct changes in the epidermal-dermal junction developed, that could be followed through early, hyperplastic and neoplastic phases. With the SEM the first changes were seen in the basal layer of the epidermis and concerned the cell arrangement. SEM provided information about the localization and development of incipient epidermal carcinomas induced by DMBA-TPA and DMBA treatment, as well as about the changes in the basal lamina. These can be classified by their surface, their extent and their frequency throughout large regions. Our studies indicate that these changes vary greatly, depending upon the treatment used and the time of their development. Only the progressive disintegration of the basal lamina is characteristic of carcinogenesis. (Author abstract) (32 Refs)

CELL CULTURE STUDIES OF MECHANISMS OF MODIFICATION

32. INITIATION OF C3H/10T1/2 CELL TRANSFORMATION BY N-METHYL-N'-NITRO-N-NITROSOGUANIDINE AND AFLATOXIN B1.

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Carcinogenesis; 3(4):391-395 1982

The utility of C3H/10T1/2 mouse embryo fibroblasts for the detection of carcinogenic substances has been limited by their apparent insensitivity to the oncogenic effects of direct-acting alkylating agents such as N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and procarcinogens such as aflatoxin B1 (AfB1). Because the process of C3H/10T1/2 transformation can be observed to proceed through discrete stages of initiation and promotion, we have considered the possibility that MNNG and AfB1 may only initiate C3H/10T1/2 transformation. Treatment of asynchronous C3H/10T1/2 cells with MNNG or AfB1 alone generally produced few transformed foci. If MNNG or AfB1 treatment was followed by the exposure of cells to the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA), numerous transformed foci were produced. Phorbol did not enhance transformation by either substance. MNNG and AfB1 thus appear to be initiating agents for transformation. TPA also enhanced the transformation of C3H/10T1/2 cells by low doses of 3-methylcholanthrene (3-MCA), but transformation by high concentrations of 3-MCA was inhibited by the presence of TPA. These studies suggest that the sensitivity of the C3H/10T1/2 transformation system to potential carcinogens can be dramatically heightened if the bioassay is conducted in the presence and absence of TPA. (Author abstract) (37 Refs)

33. TUMOR DEVELOPMENT IN THE HUMAN COLON IS ENHANCED BY EPIDERMAL GROWTH FACTOR (UROGASTRONE), DEOXYCHOLIC ACID, AND AN ENDOGENOUS ANALOG TO TPA (MEETING ABSTRACT)

Friedman EA

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Conference on Cell Proliferation, Cancer and Cancer Therapy, February 17-19, 1982, New York, New York New York Academy of Sciences; :AP-5 1982

Many human neoplasms arise through a series of progressive cellular changes. Premalignant cells in the colon form a benign tumor or adenoma, from which a carcinoma develops. Benign tumors fall into three classes based on their pathology and clinical prognosis. Premalignant epithelial cells cultured from each class reflect the tumor's position in the progression to carcinoma. Cells from early-stage (tubular) adenomas are stimulated to divide by EGF(epidermal growth factor) (structurally similar to urogastrone, a tropic hormone in the intestine), by TPA (12-O-tetradecanoylphorbol-13-acetate), and by deoxycholic acid, a secondary bile acid found in the colon. Cells from either intermediate-stage (villotubular) or late-stage (villous) adenomas are not stimulated to divide by EGF or by deoxycholic acid. TPA-treated intermediate and late-stage premalignant cells from rills and clusters several cells in thickness and secrete a plasminogen activator. This multilayering is reminiscent of areas of carcinoma found within adenomas. Furthermore, it suggests that a endogenous compound which binds to TPA receptors on late-stage premalignant cells, and so mimics

TPA activity, is important in the transition to malignancy. (no Refs)

34. 9,10-DIMETHYL-1,2-BENZANTHRACENE (DMBA) AND 12-O-TETRADECANOYL PHORBOL 13-ACETATE (TPA) INDUCED CHROMOSOME CHANGES IN PRIMARY CULTURES OF MOUSE AND HUMAN EPIDERMAL CELLS (MEETING ABSTRACT)

Broadhead J, Kinsella AR
Christie Hospital, Manchester, England
Br J Cancer; 44(2):301 1981

The classical system for the study of 2-stage carcinogenesis in vivo has been mouse skin. Primary cultures of epidermal cells isolated from neonatal BALB/c or SENCAR mouse skin are being studied in vitro. Results from this system are compared with those obtained from human keratinocytes in vitro. Chromsome changes have often been implicated in the process of neoplastic transformation. In vitro epithelial-cell systems allow this process to be followed through the stages of initiation and promotion, eventually giving rise to fully transformed cells. It is therefore possible to study chromosome changes associated with the progression towards malignancy. Primary mouse and human epidermal-cell cultures were treated with DMBA (1-200 ng/ml) or TPA (1-1000 ng/ml) and fixed in situ for chromosome analysis at later stages. Within one day of treatment with a single dose of DMBA, mouse epidermal-cell chromosomes show altered configurations such as metacentric chromosomes and chromatid fragments. Five days after treatment triradial and quadriradial formations are seen. At similar concentrations of DMBA, human epidermal-cell chromosomes show no such aberrations, but there appears to be an increase in the level of aneuploidy above that in control cultures. Addition of a single dose of TPA to any of the epidermal-cell cultures has no effect on chromosome configuration, aneuploidy or polyploidy. Autoradiographic studies are being conducted to provide data concerning the growth characteristics of the cultures at different stages following treatment. (no Refs)

35. IDENTIFICATION OF A LIVER PROTEIN WHICH BLOCKS PROMOTION OF TRANSFORMATION BY PHORBOL ESTERS (MEETING ABSTRACT)

Dion LD, Gindhart T, Colburn N
National Cancer Institute, Frederick, MD, 21701
Fed Proc; 41(3):331 1982

The JB-6 mouse epidermal cell line has been developed to study promotion of neoplastic transformation in vitro. Treatment of JB-6 cells with Phorbol Myristate Acetate (PMA) at 1 to 100 ng/ml results in the acquisition by JB-cells of neoplastic potential in nude mice and anchorage independent growth. Among the biochemical responses which occur during PMA treatment is a large (greater than 75%) and rapid (less than 4 hours) decrease in procollagen synthesis. During a study of the possible role of H2O2 in the process of promotion, it was observed that catalase purchased commercially would inhibit PMA induced promotion. This catalase preparation also blocked the PMA induced loss of procollagen in a dose dependent manner at 25 to 50 ug/ml. Highly purified catalase failed to block the PMA dependent procollagen loss suggesting the presence of another inhibitory factor in the crude material. SDS-PAGE (Sodium dodecyl sulfate-polyacrylamide gel electrophoresis) of the catalase preparation indicates in excess of 20 proteins mostly below 100,000 MW Bovine catalase (mw 60,000) appears to be the major protein band. The activity is Trypsin sensitive, and is excluded on a G-200 column along with catalase tetramers. This along with the SDS gel electrophoresis indicates a multimeric structure. Separation from catalase can be obtained by Con-A affinity chromatography. The inhibitor sensitive steps appear to occur 4 to 18 hours post PMA exposure. (no Refs)

36. INHIBITION OF PHORBOL ESTER-RECEPTOR BINDING BY A FACTOR FROM HUMAN SERUM.

Horowitz AD, Greenebaum E, Nicolaides M, Woodward K, Weinstein IB
Div. Environmental Sciences and Cancer Center, Inst. Cancer Res., Columbia Univ., New York, NY, 10032
Mol Cell Biol; 2(5):545-553 1982

The mechanisms by which a factor isolated from human serum (SF) inhibits phorbol-12,13-dibutyrate (PDBu) binding in intact monolayer cultures of the rat embryo cell line CREF N and in a subcellular system containing membranes of these cells, were studied. In addition the release induction of arachidonic acid and choline from prelabeled cellular phospholipids by PDBu was compared to that of the SF. The SF may perform a protective role in host susceptibility to carcinogenesis. (26 Refs)

37. DECREASED RESPONSE TO PHORBOL ESTERS INVOLVES A TWO-STEP PROCESS INCLUDING RECEPTOR MODULATION (MEETING ABSTRACT)

Jaken S, Phillips M, Tashjian AH
Harvard School Public Health, Boston, MA
Toxicologist; 2(1):69 1982

Tumor-promoting phorbol esters (PE) act on cells via interaction with specific membrane receptors. Escape from PE-mediated actions, possibly including tumor promotion, have been documented. We have studied the mechanisms by which cells escape from PE effects using as a model system a clonal strain of mouse pituitary cells (D16) which synthesize and secrete ACTH. PE enhance ACTH release from D16 cells 2-to 5-fold above unstimulated control levels. ED50s for this response, approx 16 nM for phorbol dibutyrate (PDBu), approx 2 nM for phorbol myristate acetate (PMA) agree closely with the apparent Kds of these ligands for the PE receptor as measured by competition for binding with [3H]PDBu. Pretreatment with PE for 2 hr resulted in a decrease in ACTH release with PE rechallenge to 23% of that from cells not pretreated (desensitization). The 2-hr pretreatment did not change the affinity of number of PE receptors nor did it decrease the responsiveness of the cells to other ACTH secretagogues (cAMP, isoproterenol). However, the continued presence of PE caused a gradual decrease in [3H]PDBu binding which was first detected at 5 hr and was maximal by 24 hr. Scatchard analysis indicated a decrease in the number of [3H]PDBu binding sites (down modulation). In these down-modulated cells, the magnitude of PE stimulation of ACTH release correlated well with the number of remaining PE-receptors. (no Refs)

38. AN EXTRA-NUCLEAR FUNCTION OF RETINOIC ACID (MEETING ABSTRACT)

Bolmer SD, Wolf G
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Fed Proc; 41(3):740 1982

Retinoids have long been known to inhibit the activity of phorbol esters in tumor promotion. In vitro studies have shown that phorbol esters cause cells to assume many, but not all, the characteristics of transformed cells. Among these are

increased deoxyglucose uptake, induction of ornithine decarboxylase (ODC), and loss of fibronectin (FN). We investigated the effect of tetradecanyol phorbol acetate (TPA) and retinoic acid (RA) on enucleated cells. In normal Swiss 3T3 cells 10(-9)-10-6M TPA caused a dose dependent increase in both ODC activity and release of FN into the cell media. Cellular FN was labeled by incubating the cells in 3H-leucine for 4 hrs, before changing the media and adding TPA+/- RA. Cells treated with 10-6M TPA for 4 hrs lost nearly twice as much FN as control cells. In cells treated with 10-6M TPA, 10(-8)-10-6M RA inhibited stimulation of ODC and loss of FN so that at 10-6M RA, the FN in the media was nearly the same as in the media of the control cells. Next, 3H-leucine labeled cells were enucleated with cytochalasin B and centrifugation. The cells were better than 90% enucleated as shown by 3H-thymidine incorporation and Giemsa stain. When the enucleated cells were treated with 10-6M TPA, they released more than 2x as much FN as did control cells. RA (10-6M) reduced the loss of FN by greater than 30%. We conclude that TPA does not require the cell nucleus to induce release of FN and furthermore that RA does not require the cell nucleus to inhibit the action of the tumor promoter. (no Refs)

39. THE MODULATING OF ONOCOGENIC TRANSFORMATION INDUCED BY AGENTS AND MODALITIES USED IN CANCER THERAPY (MEETING ABSTRACT)

Borek C
College of Physicians and Surgeons, Columbia University, New York, NY
Conference on Cell Proliferation, Cancer and Cancer Therapy, February 17-19, 1982, New York, New York New York Academy of Sciences; :A18 1982

Agents which effectively control cancer in the human may also possess a significant oncogenic potential. Cell culture systems of both rodent and human origin serve as powerful tools to study the neoplastic potentials of these agents and to evaluate factor which modulate their transforming action. Our work indicates that the initiation of neoplastic transformation in vitro by x-rays is inhibited by maintaining the cells under hypothyroid condition; that the presence of triiodothyronine at doses as low as 10-12M at the time of radiation is essential for the induction of transformation. Similar results are being seen when the transforming agents is Cis platinum. Radiation induced oncogenesis is also inhibited by a variety of vitamin A analogs. This effect is excercised at the expression phase of transformation and is associated with membrane rather than chromosome changes. Additional work indicates that the oncogenic potential of x-rays and bleomycin is inhibited by superoxide dismutase; a free radical scavenger, a fact of potential interest in cancer therapy. (no Refs)

40. EFFECT OF CHEMICAL MUTAGENS ON HERPES VIRUS-INDUCED CELLULAR TRANSFORMATION AND TESTING FOR MUTAGENESIS IN MOUSE CELLS.

Johnson FB
Dept. Microbiology, Brigham Young Univ., Provo, UT
Effect of Chemical Mutagens on Herpes Virus-induced Cellular Transformation and Testing for Mutagenesis in Mouse Cells. Available from National Technical Information Service, Springfield, VA, as AD-A102 854/7:, 17 pp., 1981.

The temperature sensitive (ts) mutant A8(293) of herpes simplex Type 2 virus (HSV-2) was employed in tests to detect chemical interactions with the virus causing increased transformation of target cells. Mouse 3T3 cells were monitored for morphological transformation. Hydrazine and 1,2-dimethylhydrazine caused an enhancement of viral transformation of between three to four fold, confirming earlier findings using ultraviolet light inactivated wild type virus. Norharman (pH-pyrido(3,4-6)indole), a component to tobacco tars, caused a nearly three-fold enhancement of transformation. Xylene and tolulene were not found to enhance viral transformation. Experiments involving host-mediated activation of the test chemicals were unsuccessful because of low target cell recovery due to inhibition of the target 3T3 cells. (Author abstract)

41. COMPARATIVE EFFECTIVENESS OF THE ANTICARCINOGENIC AND TUMOR GROWTH INHIBITORY ACTIVITIES OF LYMPHOTOXIN, AN IMMUNOLOGIC HORMONE AND LYMPHOKINE (MEETING ABSTRACT)

Evans CH, Heinbaugh JA, DiPaolo JA
National Institutes of Health, Bethesda, MD, 20205
Fed Proc; 41(3):494 1982

The ability of lymphotoxin to prevent morphologic transformation induced by uv-irradiation or chemical carcinogen was contrasted with lymphotoxin inhibition of transformed cell growth to further assess the antineoplastic properties of this lymphokine. Syrian hamster peritoneal leukocytes were stimulated with phytohemagglutinin for 24 hr, the lymphokines diafiltered, and lymphotoxin purified by isoelectric focusing and HPLC (high performance liquid chromatography). Lymphotoxin cytolytic units were determined by measuring 3H-TdR (thymidine) release from mouse L cells. Hamster embryo cells (HEC) seeded for colony formation in culture dishes were treated simultaneously with carcinogen and lymphotoxin, and morphologic transformation quantitated after 7 days growth. Tumor producing cell lines derived from transformed colonies were cultured in reconstruction experiments with HEC and lymphotoxin, and the frequency of transformed colonies determined at 7 days. Lymphotoxin irreversibly inhibited carcinogen induced transformation with 6 units/ml reducing the transformation frequency 50%. Lymphotoxin inhibition of tumor cell growth, however, was reversible when growth following a 24 hr pulse of lymphotoxin was compared with 7 day exposure. A 50% reduction in tumor cell growth in 3 transformed lines, moreover, required 124, 330, and 477 units/ml, demonstrating that the anticarcinogenic activity of lymphotoxin can be 20+ fold greater than its tumor growth inhibitory activity. (no Refs)

EPIDEMIOLOGIC DATA CONCERNING MODIFICATION OF CARCINOGENESIS

42. ETIOLOGY OF MOUTH AND LIP TUMORS.

Zabezhinskii MA, Godorozha PD
N. N. Petrov Res. Inst. Oncology, Leningrad, USSR
Vopr Onkol; 28(2):105-113 1982

Literature data on the etiology of mouth and lip cancers are reviewed. Pathogenesis of mouth neoplasms is associated with the exposure to various chemical, physical, and biological carcinogenic factors alone or in combination with the modifying factors. The increased incidence of mouth cancer can be caused by smoking, tobacco chewing, exposure to polycyclic aromatic hydrocarbons, alcohol consumption, and exposure to pesticides. Physical carcinogens include UV, x rays, and sunlight. Experimental data indicate that herpes virus and po-

lyoma virus can induce adenomas and adenocarcinomas of mouth mucosa. Poor hygiene of the mouth can increase the risk of development of mouth cancer. Chronic irritation of the mouth mucosa was shown to enhance penetration of carcinogens into mucosa and to stimulate cell proliferation. Bacterial flora of the oral cavity was shown to contribute to the metabolism of chemical carcinogens. Deficiency of vitamins A and B led to development of precancerous conditions of the mouth mucosa. (74 Refs) (In RUS)

43. CURRENT CONCEPTS OF THE ETIOLOGY AND PATHOGENESIS OF LUNG CANCER.

Chaklin AV, Gritsiute LA
No affiliation given
Vopr Onkol; 28(2):3-9 1982

Literature data on the role of smoking and environmental pollutants in the etiology of lung cancer (LC) are reviewed. Epidemiological studies showed the relationship between the smoking and incidence of LC. LC morbidity in 45-64 yr old men increased from 1.4 per 100,000 for nonsmokers to 5.9 for those who smoked <5 cigarettes/day, 13.5 for those who smoked 6-16 cigarettes/day, 29.5 for those who smoked 25-56 cigarettes/day, and 47.4 for those who smoked greater than 56 cigarettes/day. Carcinogenicity of tobacco tar is associated with the presence of polycyclic hydrocarbons, N-nitrosamines, vinyl chloride, phenols, and various co-carcinogens. Recent studies showed the carcinogenic effect of 'passive' smoking. Increased LC morbidity in the regions with intensive chemical industry indicates the co-carcinogenic effect of such air pollutants as sulfur dioxide. Pathogenesis of LC is associated with the history of chronic lung inflammation, tuberculosis, scleroderma, exposure to asbestos, immunologic suppression, and individual activity of aryl hydroxylase. (45 Refs) (In RUS)

44. CANCER AND ALTERNATING MAGNETIC FIELD EXPOSURE (MEETING ABSTRACT)

Wertheimer N
Department of Preventive Medicine, University of Colorado Medical School, Denver, CO
148th National Meeting of the American Association for the Advancement of Science, January 3-8, 1982, Washington, D.C. American Association for the Advancement of Science 182 pp., 1982.

Cancer was associated with high-current wiring configurations (HCCs) near the home for both children and adults. Such wiring can produce alternating magnetic field (AMF) exposure at a level which, though very low, may produce physiological effects. Several patterns in the data suggest that the observed association is causal rather than artifactual: (1) A dose-relationship was found. (2) The association did not appear to be an artifact of age, urbanicity, neighborhood, or socioeconomic level. (3) The association was most clearly demonstrable where urban/industrial carcinogens were least apt to obscure the effect. (4) Indices of AMF exposure based on occupational, geographic, and urbanicity variables, as well as on HCCs, consistently showed certain types of cancer (notably cancer of the nervous system) to be most strongly associated with AMF exposure. (5) A distinct pattern of latency between first exposure to the HCC and cancer diagnosis was seen. This pattern suggests that AMFs act as promoters rather than initiators of cancer. Such a cancer-promoting effect is further suggested by preliminary work which indicates that residence at a HCC home may be associated with a relatively poor final prognosis for five-year survivors of life-threatening forms of cancer. (no Refs)

REVIEWS AND OTHER RELATED STUDIES

45. METABOLISM OF CHEMICAL CARCINOGENS.

Weisburger JH, Williams G
American Health Foundation, Naylor Dana Inst. for Disease Prevention, Valhalla, NY
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

Chemical carcinogens are defined by their ability to induce tumors, four types of response have generally been accepted as evidence of tumorigenicity. These include an increased incidence of the tumor types occurring in controls, the occurrence of tumors earlier than in controls, the development of types of tumors not seen in controls, and an increased multiplicity of tumors in individual animals. Examples of the genotoxic carcinogen class include alkylating agents which are activation independent, aromatic amines and polycyclic aromatic hydrocarbons which are activation-dependent, and metals. Examples of the epigenetic carcinogen class include plastics and asbestos, estrogen, androgen, purine analog, and phorbol ester. Promotors are agents that increase the tumorigenic response to a carcinogen when applied after the carcinogen. Genetic factors, sex and endocrine status, age, diet, activities of intestinal flora, the presence of other chemicals, the mode and frequency of exposure, and numerous other factors influence the variation in carcinogen metabolism. Research during the last few decades has pinpointed natural products as major causes of cancer in humans in various parts of the world. (486 Refs)

46. SEQUENTIAL ASPECTS OF CHEMICAL CARCINOGENESIS: SKIN.

Berenblum I
Weizmann Inst. Science, Rehovot, Israel
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

The two-stage hypothesis, the initiation-promotion hypothesis, was based on animal studies of sequential stages of skin carcinogenesis. Initiators for skin carcinogenesis include 2-acetylaminofluorene, UV light, beta-radiation, certain metabolites of 'complete' carcinogens, various alkylating agents and mutagens. Promoters for skin carcinogenesis include physical agents, 'complete' chemical carcinogens, non- or weakly-acting skin carcinogens, croton oil, straight-chain N-alkanes, phenolic compounds, extracts of tobacco leaf, and extracts of tobacco smoke condensates. The two-stage system in skin carcinogenesis has been extended, based on further experiments. Evidence that a mutational change in the DNA genome was responsible for the initiating change of carcinogenesis is based on the ability of most carcinogens to bind with DNA and that there is a fairly good correlation between mutagenic and carcinogenic properties among a wide range of compounds. Evidence for the stimulation of synthetic processes in the cell includes the stimulation of DNA and RNA synthesis as well as protein and phospholipid synthesis. The effects of enzymatic functions in the cell are based on an increase in proteinase activity, on stimulation of ornithine decarboxylase activity, on changes in cyclic nucleotide levels, and on a decrease in histidase activity. (378 Refs)

47. REACTIVE METABOLITES AS KEY INTERMEDIATES IN PHARMACOLOGIC AND TOXICOLOGIC RESPONSES: EXAMPLES FROM CHEMICAL CARCINOGENESIS.

Miller EC, Miller JA
McArdle Lab. for Cancer Res., Univ. Wisconsin, Madison, WI, 53706
Adv Exp Med Biol; 136(partA):1-21 1982

Electrophilic reactants as toxic agents, mechanism of chemical carcinogenesis, and metabolic activation of chemical carcinogens (CC) and of 1'-hydroxyestragole (HE) are discussed. Current data on carcinogenesis indicate that the first stage, initiation, depends on the reaction of a strong electrophilic reactant (ER) with DNA and a resultant mutation of the DNA. The second stage, promotion, requires a prolonged time for completion and appears to be reversible in the early phases. The activation reactions of critical importance in the induction of tumors are influenced by the many factors (molecular geometry, polarity) that determine the approach of the procarcinogen or proximate carcinogen to the enzyme(s), the properties of the enzyme(s) in relation to the particular substrate, and the susceptibility of ER to inactivating reactions before they reach the critical target for the induction of neoplasia. Examples of some reactions for the activation of procarcinogens to ER are summarized and the metabolic activation of a broader range of CC is shown. The characterization of the DNA adducts formed from HE was studied in mouse liver. Co-chromatography in three system showed the apparent identity of the principal products formed in vivo with the principal products formed by reaction of 1'-acetoxyestragole with deoxyguanosine (3 products) and deoxyadenosine (1 product). Data suggested that each of the deoxyguanosine adducts was substituted on the exocyclic amino group. The mutagenic and carcinogenic responses of cells to the attack by chemicals depend on the genes in the DNA that are affected, the susceptibility of the modified nucleic acid residues to repair, the fidelity of the repair, and the effects of unrepaired lesions on DNA replication. (56 Refs)

48. RETINOIDS, URINARY BLADDER CARCINOGENESIS, AND CHEMOPREVENTION: A REVIEW AND SYNTHESIS.

Lower GM, Kanarek MS
Dept. Veterinary Science, Coll. Agricultural and Life Sciences, Univ. Wisconsin, 1655 Linden Drive, Madison, WI, 53706
Nutr Cancer; 3(2):109-115 1981

An analysis of the effects of natural (vitamin A) and synthetic retinoids on experimental carcinogenesis of the urinary bladder indicates that inhibitory activity is carcinogen- or carcinogen-class-specific. These findings suggest that there may be more than one pathway for the neo-differentiation of urothelial cells to frank carcinoma and that these pathways may be related to both carcinogen class and dietary vitamin A status. (Author abstract) (54 Refs)

49. LYMPHOTOXIN. AN IMMUNOLOGICAL HORMONE WITH ANTICARCINOGENIC AND ANTITUMOR ACTIVITY.

Evans CH
Tumor Biology Section, Lab. Biology, NCI, Room 2A17, Building 37, Bethesda, MD, 20205
Cancer Immunol Immunother; 12(3):181-190 1982

Anticarcinogenic and antitumor activities of lymphotoxin (LT), one of the immunologic hormones secreted by activated WBC, are reviewed. When 10(5) 104C1 guinea pig cells transformed by benzo(a)pyrene were mixed with lymphokine (LK) medium containing 150 units LT and the cells administered to a syngeneic guinea pig, the tumor outgrowth was retarded compared with untreated transformed cells. LK preparations probably contained a number of LK in addition to those that were measured. The variety of data suggests that one or more LK can by direct or indirect mechanisms inhibit tumor growth, although the identity, interrelationships, and comparative activities of the responsible LK remain to be established. The fourth class of cytotoxic LK is the LT. A number of forms or components ranging from approx 12,000-1,200,000 mol wt have been reported. LT can be produced by mitogen or antigen stimulation of WBC for periods ranging from 4-8 hr to 5-7 days. LT is generated by the culture of 10(7) lymphoid cells from lymph nodes, peripheral blood, spleen, or other WBC populations from humans or experimental animals for a period of 24 hr in serum-free medium with antigen or mitogen to activate the cells. Guinea pig and Syrian hamster LK can be produced with no detectable interferon (INF) activity. Hamster LK preparations induced by phytohemagglutinin (PHG), fetal bovine serum, Concanavalin A, or antigenic stimulation with key-hole limpet hemocyanin of peritoneal or spleen WBC contain no INF activity, with the LT units in the preparation varying over more than a 50-fold range. Biological activity of LT is in inducing an irreversible inhibition of carcinogen-induced morphological transformation in vitro. The anticarcinogenic activity of LT preparations is inhibited by galactose and PHG, indicating that the activity is due to LT. LT has a possible significance in preventive oncology, cancer therapy, and in general medicine and biology. (64 Refs)

50. HEREDITARY ADENOMATOSIS OF THE COLON AND RECTUM: RELEVANCE TO CANCER PROMOTION AND CANCER CONTROL IN HUMANS.

Kopelovich L
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Cancer Genet Cytogenet; 5(4):333-351 1982

Means of detecting persons at risk for colorectal cancers are described. SF cells, derived from normal-appearing biopsies of ACR gene carriers, appear to exist in an initiated state as the result of a dominant mutation. Topics discussed in relation to ACR and SF cells and colorectal neoplasms include the following: membrane-associated parameters, metabolic alterations, differential susceptiblity to transformation by chemical and physical agents and oncogenic viruses, cancer-related antigens, tissue culture studies, tumor promotion, genetic mechanisms, and cancer prognosis and control. (141 Refs)

51. HOST AND ENVIRONMENTAL FACTORS ENHANCING CARCINOGENESIS IN THE RESPIRATORY TRACT.

Nettesheim P, Topping DC, Jamasbi R
Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC, 27709
Annu Rev Pharmacol Toxicol; 21:133-163 1981

Selected laboratory studies conducted during the last decade that exemplify what has been learned about the multicomponent etiology of lung cancer are reviewed. Sections concerning experiments relating to modification of host susceptibility include the following: studies on age specific susceptibility of respiratory tract epithelium to carcinogens, effect of immune suppression on the development of respiratory tract tumors, role of dietary vitamin A in the susceptibility to lung cancer induction, and role of respiratory tract infections in the pathogenesis of lung cancer. Sections concerning the interaction of

environmental or occupational agents include: two stage carcinogenesis in respiratory tract epithelium, cocarcinogenic effects of chrysotile asbestos, role of so-called inert particles in respiratory tract carcinogenesis, nickel subsulfide as a possible cocarcinogen in occupational lung cancer, studies on benzo(e)pyrene as a cocarcinogen, and role of irritant gases and vapors as cocarcinogens in the respiratory tract. (117 Refs)

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4. EXPERIMENTAL TUMORS OF THE PERIPHERAL NERVOUS SYSTEM.
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Cancer Res. Center, Tbilisi, USSR
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6. DIETHYLSTILBESTROL: EFFECT OF IN UTERO EXPOSURE.
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Am J Obstet Gynecol; 142(7):905-921 1982

8. BIOLOGICAL EFFECTS OF MINERAL WOOL.
Petersen R, Ehrhorn H, Mousing K, Sabroe S, Silberschmid M, Venstrup-Nielsen SE
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Dept. Viticulture and Enology, Univ. California, Davis, CA
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Cancer; 49(10):1970-1984 1982

11. THE BIOLOGICAL EFFECTS OF CARRAGEENAN AND OTHER SULFATED POLYSACCHARIDES WITH PARTICULAR ATTENTION TO IMMUNOLOGICAL AND CARCINOGENIC PROPERTIES.
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Marine Science Lab., Ministry for Conservation - Victoria, P.O. Box 114, Queenscliff, Victoria 3225, Australia
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24. REGULATION OF GENE EXPRESSION IN NORMAL AND NEOPLASTIC CELLS. A REVIEW.
Hochhauser SJ, Stein GS, Stein JL
Dept. Biochemistry and Molecular Biology, Univ. Florida, Coll. Medicine, Gainsville, FL, 32610
Pathobiol Annu; 11:1-29 1981

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Karelina TV
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Natl. Cancer Res. Inst., Tsukiji, Tokyo, Japan
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Eksp Onkol; 4(2):3-12 1982
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33. THE PERSISTENCE OF RETROVIRUSES.
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Griffin BE
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Symp Soc Gen Microbiol; 33:227-247 1982

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Seemayer TA, Oligny LL, Gartner JG
Dept. Pathology, Montreal Children's Hosp., Montreal, Quebec, Canada
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Groopman JE, Gottlieb MS
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Pliss GB, Turusov VS, Zabezhinskii MA
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Zaklad Genetyki Czlowieka, PAN, 60-479 Poznan, Poland
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MODIFICATION OF CARCINOGENESIS

SERIES CK04 No. 82/11

NOVEMBER, 1982

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MODIFICATION OF CARCINOGENESIS BY CHEMICAL AGENTS OR IRRADIATION

1. SELENIUM AND THE ACUTE EFFECTS OF THE CARCINOGENS, 2-ACETYLAMINOFLUORENE AND METHYLAZOXYMETHANOL ACETATE.

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Cancer Res; 42(8):2985-2989 1982

Selenium inhibits the development of 2-acetylaminofluorene-induced hepatic tumors and methylazoxymethanol-induced colon tumors. It has been suggested that selenium exerts these protective effects by inhibiting metabolic activation of the carcinogen. We have studied the effects of selenium upon the acute inhibition of RNA and DNA synthesis induced by 2-acetylaminofluorene or methylazoxymethanol in intact liver, regenerating liver, and colon of weanling male Sprague-Dawley rats. Some animals received selenium in the drinking water (4 ppm) for 1 wk, while others received a single injection of selenium (1 mg/kg ip) prior to being treated with the carcinogens. No protection against the effects of the carcinogens on RNA

HE 20.3173/2:

or DNA synthesis was noted with either treatment of selenium. Disulfiram did protect against the 2-acetylaminofluorene-induced inhibition of hepatic RNA synthesis, and pyrazole prevented the inhibition of RNA synthesis induced by methylazoxymethanol in both liver and colon. Serum selenium levels are reported. The data indicate that selenium does not influence the acute alterations induced by the carcinogens 2-acetylaminofluorene or methylazoxymethanol and suggest that the tumor-preventive effects of selenium are probably due to a mechanism other than interference with carcinogen activation and interaction with cellular macromolecules. (Author abstract) (34 Refs)

2. EFFECT OF SELENIUM ON THE INDUCTION OF BREAST FIBROADENOMAS BY ADENOVIRUS TYPE 9 AND 1,2-DIMETHYLHYDRAZINE-INDUCED BOWEL CARCINOGENESIS IN RATS.

Ankerst J, Sjogren HO
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Int J Cancer; 29(6):707-710 1982

Selenium in its organic and inorganic forms has been shown to inhibit the development of chemically induced, spontaneous and transplanted tumors. The present investigation was performed to study the effect of selenium (4 ug per ml of drinking water) on tumorigenesis of adenovirus-type-9-induced breast fibroadenomas and on 1,2-dimethylhydrazine-induced bowel carcinogenesis in WF rats. It was found that identical treatment with Se under identical conditions and with no obvious toxic effects on the rats (1) resulted in inhibition of DMH-induced large-bowel carcinogenesis; (2) facilitated induction of small-bowel cancer by the same carcinogen in the same animals, and (3) greatly facilitated induction of breast fibroadenoma by adenovirus Type 9 in the same strain of rats. The effect of Se treatment on DMH-induced large-bowel carcinogenesis confirms previous findings and proves that the opposite effect on fibroadenoma development is not due to differences in eg effective dose, animal strains or condition of the animals. It is not yet clear through which mechanisms Se exerts these effects. (Author abstract) (29 Refs)

3. DIFLUOROMETHYLORNITHINE (DFMO) DIMINISHES 1,2-DIMETHYLHYDRAZINE-INDUCED (DMH) COLONIC CARCINOGENESIS IN MICE (MEETING ABSTRACT).

Kingsnorth AN, King WW, McCann PP, Diekema K, Ross JS, Malt RA
Department of Surgery, Harvard Medical School, Boston, MA, 02114
Gastroenterology; 82(5,part2):1100 1982

Effects of specific irreversible inhibition of ornithine decarboxylase (ODC) with DFMO were evaluated in view of evidence directly linking the intensity of cell proliferation to DMH-carcinogenesis. Male CDI mice (168) were injected weekly with DMH (20mg/kg) for 28 weeks with or without 1% DFMO in the drinking water. DFMO (mean intake 2.8g/kg/day) caused 93% inactivation of colonic ODC activity. Thirty minutes before death at 28 weeks all animals received an sc injection of 25 uCi [3H]methyl-thymidine. Full thickness specimens of colon were analyzed later for ODC, polyamines, DNA content, RNA content, DNA specific activity, crypt depth, and number of tumors. Throughout the 28 weeks of the experiment, DMH-treated mice had similar colonic ODC activity to controls. At 28 weeks RNA content was increased 8.6%, DNA content 10%; and DNA specific activity 24% in DMH-treated mice. RNA:DNA ratio in DMH-treated mice was the same as in controls. Mice receiving DMH and DFMO had no increase in crypt depth. Crypt depth in mice taking DFMO alone was also the same as controls. After 28 weeks treatment with DFMO there was a fall in putrescine (PUT) content (46-63%); a fall in spermidine (27-38%) and a rise in spermine (18-22%). PUT was 31.3% higher in DMH-treated mice than controls. At 28 weeks 13 out of 17 mice (76%) treated with DMH alone had histologically confirmed colon tumors. Two out of 18 (11%) mice treated with DMH and DFMO had colon tumors. Fifty colon carcinomas were present in 16 DMH-treated mice; a total of 3 colon tumors was present in 3 of the mice treated with DMH and DFMO. Inactivation of colonic ODC by continuous feeding of DFMO results in partial depletion of cellular polyamines and a greatly reduced incidence of DMH-induced colon carcinomas. (no Refs)

MODIFICATION OF CARCINOGENESIS BY DIETARY COMPONENTS OR DIGESTIVE FACTORS

4. INFLUENCE OF DELAYED ADMINISTRATION OF RETINYL ACETATE ON MAMMARY CARCINOGENESIS.

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Cancer Res; 42(7):2639-2643 1982

Administration of a dietary retinoid supplement beginning 1 wk after carcinogen administration is highly effective in the inhibition of rat mammary carcinogenesis. A study was designed at two carcinogen dose levels to determine to what extent retinoid feeding can be delayed and retain its chemoprotective effect. In the high-dose experiments, groups of 30 virgin female Sprague-Dawley rats received a single iv dose of 50 mg N-methyl-N-nitrosourea (MNU) per kg body wt and were fed a dietary supplement of 328 mg retinyl acetate per kg diet beginning at 1, 4, or 8 wk after MNU administration. In the low-dose experiment, groups of 50 rats received 25 mg MNU per kg, and the retinoid was begun at 1, 4, 8, 12, 16, or 20 wk post-MNU. Controls at both dose levels received a placebo diet beginning 1 wk after carcinogen treatment. At the high MNU dose, retinyl acetate was most effective in inhibition of carcinogenesis when treatment was begun 1 wk after MNU administration. Delaying retinyl acetate feeding until 4 wk post-MNU resulted in slightly reduced chemoprotective efficacy, while an 8-wk delay caused a complete loss of anticancer activity. At the low MNU dose, delaying retinyl acetate administration for up to 12 wk after MNU administration caused no loss of chemopreventive efficacy. A 16-wk delay resulted in decreased anticancer activity, while retinoid treatment begun 20 wk post-MNU had no effect on cancer induction. Retinoid administration can be delayed beyond 1 wk and retain its activity against rat mammary carcinogenesis; the length of delay allowable without loss of activity is a function of tumor latency. (Author abstract) (15 Refs)

5. EXPERIMENTAL INDUCTION OF C CELL TUMOURS IN THYROID BY INCREASED DIETARY CONTENT OF VITAMIN D3.

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Acta Endocrinol (Copenh); 100(1):41-45 1982

Neonatal Wistar rats were given either 0, 5 or 10 uCi 131I within 24 hr of birth. Following weaning, they were fed a diet high, normal or deficient in vitamin D, for up to 2 yr. Animals were sacrificed at approx 3 monthly intervals, and serial sections of thyroid scanned for C cell tumors following calcitonin localization. Plasma calcium levels were also measured, and all results statistically analyzed. As expected, those animals given the high vitamin D had significantly raised calcium levels over those on a normal D diet, whilst those given a low D diet had lower calcium levels than normal. Analysis of the incidence of C cell tumors showed that those given a high D diet had significantly more C cell tumors, whilst those on a low D diet had significantly fewer than normal. Radiation dose also influenced C cell tumor incidence. There was a significant relationship between the vitamin D content of the diet and the incidence of C cell tumors, with those animals on a high D diet having the largest number of tumors. It is suggested that vitamin D or its metabolites may directly promote C cell growth, and that the high incidence of C cell tumors in the normal laboratory rat reflects the artificially high vitamin D content of the laboratory rat diet. The dietary vitamin D content may also be relevant to the variation in geographical incidence of medullary carcinoma in man. We consider it likely that vitamin D metabolites may play a significant role in the control of C cell function, hyperplasia and tumor formation in the rat, and that this may be more important in tumor formation than the role of serum calcium variation. (Author abstract) (20 Refs)

MODIFICATION OF CARCINOGENESIS BY HORMONAL OR GENETIC FACTORS

6. INFLUENCE OF DAILY SUBCUTANEOUS ADMINISTRATION OF 6-METHYLPREDNISOLONE AND ORAL APPLICATION OF 30% SALINE SOLUTION ON TUMORIGENESIS INDUCED IN MOUSE STOMACH BY SINGLE APPLICATION OF 7,12-DIMETHYLBENZ(A)ANTHRACENE.

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J Cancer Res Clin Oncol; 103(2):207-209 1982

Low-dose dimethylbenz(a)anthracene (25 mg/kg po by gavage on day 1) produced papillomas in the forestomach of female C57BL/6 mice treated with 6-methylprednisolone (MP: 80 mg/kg/day sc on days 1-3) and 30% NaCl (0.25 ml/animal, days 1-3, 1 hr after MP, by gavage). Hyperplasia/hyperkeratosis was observed in 5/20 animals and papilloma in 12/20 animals. Median latent period for papilloma development was 25 days. The results indicate that in an altered environment small amounts of a chemical carcinogen suffice to induce tumors. (7 Refs)

MODIFICATION OF CARCINOGENESIS BY VIRUSES, BACTERIA OR IMMUNE SYSTEM COMPONENTS

7. INHIBITION OF 7,12-DIMETHYLBENZ(A)ANTHRACENE-INDUCED TUMORS IN SYRIAN HAMSTERS BY PRIOR INFECTION WITH H-1 PARVOVIRUS.

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Cancer Res; 42(7):2552-2555 1982

Hamsters, given injections, sc at birth of H-1 parvovirus and 1 mo later given a single injection of 7,12-dimethylbenz(a)anthracene, had a 38% tumor incidence compared with a 95% incidence in animals receiving 7,12-dimethylbenz(a)anthracene alone. Thus, H-1 which, it has already been shown, invokes a resistance to the incidence of spontaneous and adenovirus-induced neoplasms in hamsters also produces a suppression of a carcinogen-induced tumor in these animals; this suggests that the H-1-induced barrier to successful oncogenesis by these diverse agents has a common mechanism which, present experiments indicate, is not related to a positive or negative H-1 serology. The pathology of the 7,12-dimethylbenz(a)anthracene-induced tumors was similar for both control and H-1-infected hamsters. Although all but one of the primary neoplasms were anaplastic fibrosarcomas as reported previously by others, 25% of the affected females had, in addition, mammary adenocarcinomas, an extremely rare tumor in hamsters. (Author abstract) (26 Refs)

8. BILE ACIDS AND COLORECTAL CARCINOMA: NEW ASPECTS OF ETIOLOGY (MEETING ABSTRACT)

Schwering H, Tentrup B, Hobik HP, Strunk E

Surgical Clinic, Muenster University and Institute of Pathology of Clemens-Hospital, Muenster, W. Germany

International Congress of Colo-proctology, November 2-4, 1981, Prague, Czechoslovakia. European and Mediterranean Association of Colo-proctology 107 pp., 1981.

Etiologic studies of human colorectal carcinoma suggested that the cocarcinogenic effect of bile acids depends on the presence of desoxidizing bacteria (certain anaerobic subclasses of bacteroides) capable of metabolizing cholic acid to desoxycholic acids. Experimental DMH (dimethylhydrazine) carcinoma resembles human colorectal carcinoma in terms of localization and formal pathogenesis: the animals develop primary mucus-producing carcinomas or adenocarcinomas arising from adenomatous polyps. A special model was developed to verify the hypothesis of bile acid/bacterial cocarcinogenesis. In male Wistar rats the transversal and descendent parts of the colon were interposed into the upper jejunum. Closing the right flexure in a blind pouch, a proximal jejuno-transversostomy was made end-to-side in the middle of the transversum, then a distal descendo-jejunostomy end-to-end. Colonic continuity was restored by end-to-side ascendo-sigmoidostomy. The operated animals and unoperated controls were treated similarly with DMH. Cancerization was found to be considerably accelerated in the operated group. Macroscopic and microscopic findings in the interposed colon segments were compared with those in other colonic segments of the same animal: Tumorigenesis was found to start in the interposed colon, and to show a distinct phase shifting in comparison to sequential tumor development in the residual colon. Operated animals without DMH treatment developed carcinomas in the interposed colon segment one year after surgery. (no Refs)

OTHER STUDIES OF THE MODIFICATION OF CARCINOGENESIS

9. TUMORIGENESIS AT A PREDETERMINED ORAL SITE AFTER ONE INTRAPERITONEAL INJECTION OF N-NITROSO-N-METHYLUREA.

Konstantinidis A, Smulow JB, Sonnenschein C
Dept. Stomatology, Dental Sch., Univ. Thessaloniki, Thessaloniki, Greece
Science; 216(4551):1235-1237 1982

Tumors in the soft tissues of the oral cavity of rats developed at predetermined sites as a result of a combination of an intraperitoneal injection of a direct-acting carcinogen, N-nitroso-N-methylurea, and a continuous irritation of the buccal mucosa by a stainless steel wire. The incidence of histologically malignant tumors was significantly higher in the irritated area than in any other area of the body. These results constitute evidence for a carcinogenic mechanism whereby the cells that develop into tumors may require the promotional effect of a nonspecific, nonmutagenic stimulus. (Author abstract) (26 Refs)

10. EFFECT OF OVARIECTOMY AT DIFFERENT AGES ON THE INCIDENCE OF 7,12-DIMETHYLBENZ(A)ANTHRACENE-INDUCED MAMMARY HYPERPLASTIC ALVEOLAR NODULES IN FEMALE RATS.

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IRCS Med Sci [Cancer]; 9(9):778 1981

The effect of ovariectomy at birth on the incidence of mammary hyperplastic alveolar nodules in female rats was compared with ovariectomy performed at 28 and 114 days of life. The incidence of hyperplastic alveolar nodules was significantly decreased in mammary glands of female rats following ovariectomy at day 1 and 28 when compared with the respective sham-operated groups. Ovariectomy performed at day 114 showed very little effect on the mammary noduligenesis. Ovariectomy at birth produced the greatest effect. (5 Refs)

11. INFLUENCE OF AGE ON HEPATOCARCINOGENESIS IN RATS INGESTING DIETHYLNITROSAMINE.

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Dept. Pathology, Cancer Res. Inst., Sapporo Medical Coll., Sapporo 060, Japan
Tumor Res (Sapporo); 16:19-28 1981

The effect of increasing age on the incidence of hepatocellular carcinoma induced in male Fischer rats by diethylnitrosamine (DEN) was investigated. The av amounts of daily intake of DEN per rat in Group I (3 mo old), II (6 mo old), III (9 mo old) and IV (12 mo old) were 0.77, 1.16, 0.83, and 1.03 mg, and total amounts were 53.6, 81.0, 57.8, and 72.2 mg, respectively. All rats in Group I had liver tumors larger than 5 mm in diameter. The av number of tumors larger than 5 mm in diameter in Group I was 8.30. In Group II, 75% of rats had tumors larger than 5 mm, the av number of which was 2.25 per rat. In Group III, 60% of rats had tumors larger than 5 mm. Av number of tumors per rat was 1.80. In Group IV, 63% of rats had tumors larger than 5 mm, the av number of which was 2.00 per rat. Differencet were statistically different between Group I and Group II-IV. The mechanisms by which older animals are more refractory to DEN induction are discussed. (27 Refs)

12. EFFECT OF HEMITHYROIDECTOMY AND 3-AMINO-1,2,4-TRIAZOLE ON THYROID TUMORS INDUCED BY N-BIS(2-HYDROXYPROPYL)-NITROSAMINE IN RATS.

Iwata C
First Dept. Pathology, Nara Medical Univ., Nara, Japan
Nara Igaku Zasshi; 32(6):670-684 1981

Thyroid tumors were induced in male Wistar rats administered 70 mg/100 g body wt of N-bis(2-hydroxypropyl)nitrosamine (DHPN), and the effects of 3-amino-1,2,4-triazole (amitrole) on the tumors were studied. Rats were given the DHPN 1x/wk for 4, 8, 12, 16, and 20 wk with or without undergoing hemithyroidectomy at day 10. Thyroid tumors developed in 10/20 rats given DHPN alone. Thyroid tumors also occurred in rats given DHPN and hemithyroidectomy. Amitrole (2,000 ppm, po) was administered to 11 rats for 12 wk following treatment with DHPN (1x/wk x 4), and the following 4 wk the rats were given a stock diet. Thyroid tumors developed in 10/11 rats. Results indicated that amitrole did not induce thyroid tumors when given alone, but amitrole and hemithyroidectomy, in combination with DHPN, increased the development of thyroid tumors compared to administration of DHPN alone. (37 Refs) (In JPN)

13. INTESTINAL ADAPTATION AND EXPERIMENTAL CARCINOGENESIS AFTER PARTIAL COLECTOMY. INCREASED TUMOUR YIELDS ARE CONFINED TO THE ANASTOMOSIS.

Williamson RC, Davies PW, Bristol JB, Wells M
Univ. Dept. Surgery, Bristol Royal Infirmary, Bristol BS2 8HW, England
Gut; 23(4):316-325 1982

Small-bowel resection enhances experimental colorectal carcinogenesis, probably by stimulating epithelial cell proliferation. The possibility that similar mechanisms might explain metachronous large-bowel cancers in man was tested in Sprague-Dawley rats submitted to partial colectomy before or after a 5-wk course of azoxymethane (total dose 50 mg/kg). The timing of operation did not affect tumor yields at 40 wk. Cecal resection augmented mucosal mass in the ileum and right colon but did not affect carcinogenesis. Right hemicolectomy only increased ileal segmental wt (by 22%); left hemicolectomy increased the protein and DNA contents of the residual right colon by 18-42%. Large-bowel tumors in 84 rats were distributed as follows: proximal colon 36, colonic anastomosis 51, distal colon 87, rectum 43. Consistent with this left-sided predominance, left hemicolectomy reduced the number of large-bowel tumors. A twofold increase in distal tumors after both transection and right hemicolectomy simply reflected the high incidence of anastomotic tumors. Furthermore, one rat given vehicle as opposed to carcinogen developed an invasive mucinous adenocarcinoma at the colorectal anastomosis, after left hemicolectomy. The large bowel shows limited adaptation to partial resection and is not at increased risk of carcinogenesis, except in the region of the suture line. (Author abstract) (48 Refs)

14. ENHANCEMENT OF DMBA INDUCED MAMMARY TUMOURS BY INTERMITTENT WHOLE BODY HYPERTHERMIA (42 C).

Lahiri T, Deomina N, Dedov II, Lahiri P
Chittaranjan Natl. Cancer Res. Centre, Calcutta, India
Endocrinol Jpn; 28(5):569-574 1981

Effects of intermittent whole body hyperthermia (42 C) on dimethyl benz-anthracene (DMBA)-induced rat mammary tumors were determined in terms of tumor growth, plasma hormone levels, and activity of pituitary prolactin cells. Female Wistar (50-55 days old) rats were used. Heat exposure resulted in significant growth stimulation of the tumors in the majority (16/20) of heat-treated rats, compared to rats maintained at 25 C. The growth of tumors was generally intensified after 2-3 wk of heat stress and at the end of 6 wk an approx seven-fold increase in tumor vol was observed. Histological examination revealed that 18/20 animals in the control group and 17/20 in the treated group had adenocarcinoma type tumors. Other tumors were fibroadenomas and they were not included into the study. Body wt and wt of adrenal glands in heat-exposed rats were increased, while the wt of uterus and thymus was decreased. Plasma estradiol level in heat stressed animals was lowered while values for total thyroxine and thyroid stimulating hormone showed no fluctuation. Serum prolactin level was significantly increased in the heat exposed group. An electron microscopy study of prolactin cell activity of pituitary revealed that in heat stressed animals the activity was greater than in rats maintained at room temperature. Results indicated that whole body hyperthermia definitely enhances DMBA-induced mammary tumors in rats and the differences in response pattern might be related to the mode of heat application, etiology, or hormonal sensitivity of tumors. (20 Refs)

STUDIES OF TUMOR PROMOTION OR COCARCINOGENESIS IN MOUSE SKIN

15. SIMULATED STRATOSPHERIC OZONE DEPLETION AND INCREASED ULTRAVIOLET RADIATION: EFFECTS OF PHOTOCARCINOGENESIS IN HAIRLESS MICE.

Forbes PD, Davies RE, Urbach F, Berger D, Cole C
Center for Photobiology, Temple Univ. Sch. Medicine, Skin and Cancer Hosp., 3322 North Broad St., Philadelphia, PA, 19140
Cancer Res; 42(7):2796-2803 1982

Solar ultraviolet radiation at the surface of the earth is a recognized cause of skin cancer. Postulated anthropogenic reductions in the thickness of the ozone layer would lead to an increased amount of ultraviolet radiation and hence would be expected to increase the risk of skin carcinogenesis. This study uses hairless (Skh:HR) mice as an animal model to study this increased risk. The mice were exposed 5 days/wk to graded doses of ultraviolet radiation from a xenon arc lamp attenuated by five different thicknesses of Schott glass fibers (WG320) to simulate various ozone layer thicknesses. A Robertson-Berger sunburning ultraviolet meter was used as one of the forms of dosimetry. The results of the various exposure treatments are expressed as the percentage of animal with tumors (incidence) versus time after commencing irradiation and as cumulative tumor yield (average number of tumors per survivor) versus time time. With any given filter, the time to 50% incidence is inversely related to daily dose in Robertson-Berger meter units. The time to 50% incidence for comparable Robertson-Berger meter doses through different filter thicknesses increases with increasing thickness. These results indicate that the effective dose for skin cancer induction may be estimated from the Robertson-Berger meter dose but that the Robertson-Berger meter response spectrum underestimates the photocarcinogenic effectiveness of the shorter wavelengths. The cumulative tumor yield data are also consistent with these conclusions. Alternate weighting of the source spectra with the acute-response action spectrum for mouse skin edema gave a better correlation between unit dose and time to a tumor response, independent of the source spectral distribution. This suggests that the mouse skin edema action spectrum, indistinguishable from a human skin erythema action spectrum for lambda greater than 295 nm, is similar in shape to the mouse skin photocarcinogenesis action spectrum for lambda greater than 295 nm. (Author abstract) (18 Refs)

16. MUST INITIATORS COME FIRST? TUMORIGENIC AND CARCINOGENIC EFFECTS ON SKIN OF 3-METHYLCHOLANTHRENE AND TPA IN VARIOUS SEQUENCES.

Iversen OH, Iversen UM
Inst. Pathology, Univ. Oslo, Rikshospitalet, Oslo 1, Norway
Br J Cancer; 45(6):912-920 1982

Groups of hairless mice were treated with four skin applications of 470 nmol 3-methylcholanthrene (MCA) in benzene and four of 20 nmol 12-O-tetradecanoylphorbol-13-acetate (TPA) in various sequences, twice a wk, together and separately. Three days after the last application, cell kinetic investigations were made comprising the counting of basal and suprabasal cells, the assessment of hyperplasia, the mitotic rate by the stathmokinetic method, the labeling index and the specific activity of DNA after injection of a dose of [3H]dT, and the determination of percentage of cells in each cell-cycle phase by flow cytometry. These studies showed that the various treatment schedules with four applications stimulated proliferation and caused epidermal hyperplasia, but there was no significant difference between the groups in degree of growth stimulation. There was a significantly higher tumor production by all the combinations than by MCA alone. It was of no significant importance for the tumor production whether the four applications of MCA came before or after the four of TPA. Alternating treatment (MCA-TPA, etc) seemed to give a higher risk than the other treatment sequences. The consequences of these results for the two-stage theory of carcinogenesis (stating that initiation must come first) are discussed, and it is concluded that (at least under the experimental conditions used here) initiation does not need to come first for a good tumor yield. (Author abstract) (32 Refs)

17. RETINOIC ACID PROMOTION OF PAPILLOMA FORMATION IN MOUSE SKIN.

Hennings H, Wenk ML, Donahoe R
Lab. Cellular Carcinogenesis and Tumor Promotion, NCI, Building 37, Room 3A21, Bethesda, MD, 20205
Cancer Lett; 16(1):1-5 1982

In a study to determine if inhibitors of tumor promotion could act by selectively killing initiated cells, mice were treated topically 3x weekly for 20 wk with 5.1 ug retinoic acid (RA) after initiation by a single application of 50 ug dimethylbenz(a)anthracene (DMBA), but before tumor promotion with 12-O-tetradecanoyl-phorbol-13-acetate (TPA) was begun. In the DMBA-initiated control, Group 1, no papillomas were observed during 20 wk of treatment with acetone solvent. The first papillomas were seen at wk 29, 5 wk after TPA pro-

motion had begun. At wk 44, 1 wk after the termination of TPA, 93% of the mice had developed at least one papilloma, with an av of 12 papillomas per mouse. In Group 2, initiated with DMBA and treated with RA from wk 4 to wk 23, papillomas were first seen at wk 20. By wk 24, 24 papillomas had appeared in the 29 animals. Papilloma incidence at wk 24 was the result of treatment with only DMBA and RA. With continued TPA promotion, papillomas appeared somewhat more rapidly in the RA-treated mice, indicating that RA has a definite tumor-promoting effect. (16 Refs)

18. STUDY OF PROTEIN MODIFICATIONS INDUCED BY PHORBOL ESTER TUMOR PROMOTERS IN MOUSE SKIN.

Nelson KG
Oak Ridge Associated Univ., Inc., Oak Ridge, TN
Study of Protein Modifications Induced by Phorbol Ester Tumor Promoters in Mouse Skin. Available from National Technical Information Service, Springfield, VA, as DE81031985:, 164 pp., 1981.

The purpose of this study was to determine if the phorbol ester tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) induced any specific changes in mouse epidermal proteins using the high resolution technique of two-dimensional electrophoresis. To accomplish this goal of determining the specificity and possibly the stage in promotion with which these protein changes were associated, epidermal proteins were analyzed (1) after treatment of adult mouse epidermis with several weakly promoting hyperplasiogenic agents, (2) following treatment with TPA in combination with various inhibitors of tumor promotion, (3) in basal keratinocytes isolated from adult epidermis following treatment with TPA or several weakly promoting agents, and (4) during an initiation-promotion experiment. Evidence was found which indicated that the potent tumor promoter TPA as well as the weakly promoting hyperplasiogenic agents, mezerein, ethylphenylpropiolate (EPP), and mechanical abrasion, induced similar modifications of epidermal proteins, particularly among the keratins. These keratin modifications progressed with time following treatment resulting in a keratin pattern which resembled that of newborn epidermis. (Author abstract)

CELL CULTURE STUDIES OF MECHANISMS OF MODIFICATION

19. INDUCTION OF NEOPLASTIC CELL GROWTH BY QUIESCENT CELLS IS MEDIATED BY SERUM CONCENTRATION AND CAMP PHOSPHODIESTERASE INHIBITORS.

Bertram JS, Bertram BB, Janik P
Grace Cancer Drug Center, Roswell Park Memorial Inst., Buffalo, NY, 14263
J Cell Biochem; 18(4):315-538 1982

Studies have shown that for transformed mouse fibroblasts (C3H/101/2) and Lewis lung carcinoma model systems, the expression of transformation is conditional upon the permissive behavior of neighboring cells. Such permissive behavior could be due to a failure in intercellular communication or to a failure in signal reception or processing. For a constant plating density an increase in serum concentration was shown to cause a dose responsive decrease in N-methyl-N-nitro-N-nitrosoguanidine (MNNG)-induced transformation frequency in fibroblast cells. This increase in serum concentration produced an increase in saturation density of confluent cells. A model is developed which suggests that interference in communication between cells occurs during transformation. The passage of small growth inhibitory substances through gap junctions between contacting cells controls cell cycle phase. Autonomous growth would occur through attenuation of signal intensity. This studies have identified two possible factors which may control signal strength, ie, cell density and elevated cAMP. The model thus suggests that transformed cells are deficient in their ability to form communication channels with themselves or with adjacent normal cells. The major effect of phosphodiesterase inhibitors may be to increase the latent period between tumor injection and the appearance of tumor. Applications of the model to phosphodiesterase inhibitors and to tumor promotion are discussed. (42 Refs)

20. PREVENTION AND REVERSAL BY A RETINOID OF 3,4-BENZPYRENE- AND CIGARETTE SMOKE CONDENSATE-INDUCED HYPERPLASIA AND METAPLASIA OF RODENT RESPIRATORY EPITHELIA IN ORGAN CULTURE.

Lasnitzki I, Bollag W
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Cancer Treat Rep; 66(6):1375-1380 1982

The influence of an aromatic analog of vitamin A, etretinate, on the effects of 3,4-benzpyrene and cigarette smoke condensate has been investigated in fetal mouse lung and neonatal rat tracheas grown in organ culture. In both tissues, 3,4-benzpyrene as well as cigarette smoke condensate induces a striking increase of epithelial mitosis within 12-14 days of treatment. The increase is associated with a loss of secretory activity and of ciliary function. These changes persist in the absence of benzpyrene or smoke condensate in explants transferred to control medium. Treatment with etretinate alone does not affect the normal epithelial growth rate or normal differentiation. If combined with either benzpyrene or smoke condensate, the aromatic compound inhibits the increase in cell division and prevents the loss of secretory activity or ciliary function. In explants pretreated with 3,4-benzpyrene or cigarette smoke condensate, etretinate reduces the carcinogen- or smoke condensate-induced increase in mitotic activity to normal levels and restores secretory differentiation and ciliary function. The mechanism of action involved in the anticarcinogenic activity of the retinoid is discussed. (Author abstract) (32 Refs)

REVIEWS AND OTHER RELATED STUDIES

21. CARCINOGENESIS AND BIOLOGICAL EFFECTS OF TUMOR PROMOTERS.

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Inst. Biochemistry, German Cancer Res. Center, Heidelberg, W. Germany
Carcinogenesis 7: 664 pp., 1982.

The most recent experimental findings on the etiological, cell biological, and molecular facets of carcinogenesis are reviewed. The basic problems of whether specific carcinogens function as promoters of carcinogenesis, as stimulators of initiation, or both, are addressed with respect to in vivo animal studies, epidemiological studies, and in vitro studies of tumor promotion. Carcinogenesis and tumor promotion in vivo is dis-

cussed with respect to the skin as a target tissue and nonepidermal target tissues. Effects of tumor promoters on cell proliferation and differentiation are reviewed for the epidermis and nonepidermal cell systems. Membrane interactions and receptors, effects on intercellular communication and cell metabolism, and viral and immunologic aspects are reviewed. Epidemiologic studies of esophageal cancer in Linxian County, China, nutritional carcinogenesis, and breast cancer as an example of promoting effects are discussed. (1368 Refs)

22. THE ROLE OF RADIATION AND CHEMICALS IN THE INDUCTION OF MUTATIONS AND EPIGENETIC CHANGES DURING CARCINOGENESIS.

Trosko JE, Chang CC
Dept. Human Development, Coll. Human Medicine, Michigan State Univ., East Lansing, MI, 48824
Adv Radiat Biol; 9:2-36 1981

The relationships between physical and chemical agents and their interactions and the triggering of 'regulatory dysfunction' are reviewed. The abnormal phenotype that is cancer, the multistage nature of carcinogenesis, and the classes of genetic and environmental agents affecting genetic initiation and promotion are discussed. Evidence supporting both the somatic mutation and epigenetic theories of carcinogenesis is reviewed, and an integrative model allowing for mutational and/or epigenetic mechanisms in progression of carcinogenesis is proposed. (255 Refs)

23. INHIBITION OF TUMOR INDUCTION AND DEVELOPMENT.

Zedeck MS, Lipkin M
Memorial Sloan-Kettering Cancer Center, New York, NY
Inhibition of Tumor Induction and Development. New York, Plenum Press, 233 pp., 1981.

Major aspects of chemoprevention, focusing on the inhibition of carcinogen formation, absorption, and metabolic activation and interaction with cell macromolecules, as well as prevention through immunological approaches, are outlined. Inhibition of chemical carcinogenesis by phenols, coumarins, aromatic isothiocyanates, flavones, and indoles and inhibition of carcinogen metabolisms and action by disulfiram, pyrazole, and related compounds are discussed. Retinoids and chemoprevention of cancer; ascorbic acid inhibition of N-nitroso compound formation in chemical, food, and biological systems; alpha-tocopherol and its relationship to tumor induction and development; trace elements and metals as anticarcinogens; and the protective role of plant sterols in chemical carcinogenesis are described. Immunoprevention is discussed with respect to detection of tumor-associated antigens in experimental rat bowel carcinomas, evidence that embryonic antigens are associated with bowel carcinomas, enhanced 1,2-dimethylhydrazine (DMH)-induced tumorigenesis in imunosuppressed rats, inhibitory effect on bowel carcinogenesis by immunization with transplantable syngeneic colon carcinoma and by immunization with fetal tissue, inhibition of DMH-induced carcinogenesis in multiparous rats, effects of tumor resection on the development of additional primary tumors, and regression of early primary bowel carcinomas by multimodal immunological treatment are discussed. (738 Refs)

24. THE OCCURRENCE OF CANCER IN IMMUNE DEFICIENCIES.

Penn I
Dept. Surgery, Univ. Colorado Health Sciences Center, Denver, CO
Curr Probl Cancer 6(10): 64 pp., 1982.

The association of immune deficiency states with increased cancer risk is discussed in detail. Topics covered include components of the immune system (specific immune responses, B cells, T lymphocytes, delayed hypersensitivity cells, cytotoxic T cells, helper T cells, and suppressor T cells), immune amplification mechanisms, nonspecific responses (humoral response, cellular response), immune responses to cancer (reactions deleterious to tumor growth, reactions favoring tumor growth [blocking factors, fetal antigens, alpha2-globulins, small mol wt immunosuppressive factors, suppressor cells, lack of complement]). Also discussed are mechanisms by which tumors escape immune destruction by the host, cancer in immunodeficient states, naturally occurring immunodeficient states, changes associated with organ transplantation (immunosuppressive therapy, transplanted malignancies, cancers arising de novo after organ transplantation [incidence, age and sex of patients, time of appearance of cancers, previous tumors in recipients, malignancies in the donors, types of malignancy]), multiple cancers, treatment, prognosis, effects of immunosuppression on preexisting neoplasms, cancer in uremic patients, second neoplasms arising in patients after cancer chemotherapy and radiotherapy, etiology of neoplasms in immunodeficient states, spontaneous regression of lymphomas, interferons, oncogenic viruses, oncogenic and co-oncogenic effects of immunosuppressive and cancer chemotherapeutic agents, and other potentially oncogenic treatments. (265 Refs)

25. METABOLIC EPIDEMIOLOGY OF LARGE BOWEL CANCER.

Hill MJ
Central Public Health Lab., Colindale Ave., London NW9, England
Gastrointestinal Cancer 1. Decosse JJand Sherlock P, ed. The Hague, Martinus Nijhoff Publishers, Cancer Treatment and Research, Vol. 3, 452 pp., 1981.

The epidemiology of large bowel cancer and predisposing and associated diseases are reviewed. Possible causative agents, evidence for the role of bile acids as co-carcinogens, and metabolic epidemiology via results of studies of the histopathology of large bowel cancer and the adenoma-carcinoma sequence are considered. Variables examined in relation to the development of large bowel cancer include geography, sex, socioeconomic group, race, religion, population density, time and cultural environment. Predisposing diseases include adenomatosis coli, cancer family syndrome, and colorectal adenoma. Associated diseases include associated cancers, diseases of fiber depletion, and others. Possible causative agents are stress and physical factors, radiation, immunological factors, virological factors, environmental agents, endogenous agents (cholesterol, bile acids, steroid estrogens, tryptophan metabolites, tyrosine metabolism, and N-nitroso compounds), nutrition, and genetic factors. (154 Refs)

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CHEMICAL CARCINOGENESIS

1. TOXICITY OF POLYBROMINATED BIPHENYLS (PBBS) IN DOMESTIC AND LABORATORY ANIMALS.

Damstra T, Jurgelski W, Posner HS, Vouk VB, Bernheim NJ, Guthrie J, Luster M, Falk HL
Natl. Inst. Environmental Health Sciences, Post Office Box 12233, Research Triangle Park, NC, 22709
Environ Health Perspect; 44():175-188 1982

2. CHLOROFORM: A REVIEW OF ITS METABOLISM, TERATOGENIC, MUTAGENIC, AND CARCINOGENIC POTENTIAL.

Davidson IW, Sumner DD, Parker JC
(c/o Parker) ECAO, Environmental Protection Agency, MD-52, Research Triangle Park, MD, 27711
Drug Chem Toxicol; 5(1):1-87 1982

3. FORMALDEHYDE IN PRESENT-DAY ENVIRONMENTAL TOXICOLOGY.

Beritic T, Kovac S, Dimov D
Odjel za profesionalne bolesti, Institut za medicinska istrazivanja i medicinu rada, Zagreb, Yugoslavia
Arh Hig Rada Toksikol; 32(4):363-395 1981
In SCR

4. HORMONES AS ETIOLOGICAL AGENTS IN NEOPLASIA.

Furth J
Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

5. CURRENT VIEWS ON HORMONES AND BREAST CANCER.

Molinatti GM, Limone P
Cattedra di Endocrinologia, Universita di Torino, C.so Polonia, 14, 10126 Turin, Italy
Minerva Med; 73(17):1047-1053 1982
In ITA

6. THE CHROMOSOMAL EFFECTS OF THE ORAL CONTRACEPTIVE.

Bishun NP
Tissue Culture and Cytogenetics Unit, Res. Dept., Marie Curie Memorial Foundation, The Chart, Oxted, Surrey, England
J Surg Oncol; 20(2):115-118 1982

7. TOXICITY AND CARCINOGENICITY OF NICKEL AND ITS COMPOUNDS. A REVIEW OF THE CURRENT STATUS.

Raithel HJ, Schaller KH
Institut fur Arbeits- und Sozialmedizin, Poliklinik fur Berufskrankheiten, Universitat Erlangen-Nurnberg, Schillerstrasse 25-29, D-8520 Erlangen, W. Germany
Zentralbl Bakteriol Mikrobiol Hyg [B]; 173(1/2):63-91 1981
In GER

8. HISTORICAL OVERVIEW OF NITROSOUREA DEVELOPMENT.

Goldin A
Div. Cancer Treatment, NCI NIH, Building 37, Room 5E20, Bethesda, MD, 20205
INSERM Symp; 19:3-11 1981

9. PATHOLOGY.

Goyer RA
Natl. Inst. Environmental Health Sciences, Research Triangle Park, NC
JAMA; 247(21):2973-2975 1982

RADIATION CARCINOGENESIS

10. IDENTIFYING THE HEALTH RISKS FROM VERY LOW-DOSE SPARSELY IONIZING RADIATION.

Dreyer NA, Friedlander E
Epidemiology Resources, Inc., P.O. Box 57, Chestnut Hill, MA, 02167
Am J Public Health; 72(6):585-588 1982

11. RISK OF RADIOLOGICAL EXAMINATIONS.

Jankowski J
Instytut Medycyny Pracy w Lodzi, ul. Olowiana 6, 91-614 Lodz, Poland
Pol Przegl Radiol; 45(6):383-386 1981
In POL

12. RADIOBIOLOGY OF RISK ESTIMATES IN MEDICAL IRRADIATION (MEETING ABSTRACT)

Rossi HH
Columbia University, New York, NY
IN: 148th National Meeting of the American Association for the Advancement of Science, January 3-8, 1982, Washington, D.C American Association for the Advancement of Science 182 pp., 1982.

13. RADIATION-INDUCED VASCULAR INJURY AND ITS RELATION TO LATE EFFECTS IN NORMAL TISSUES.

Law MP
MRC Cyclotron Unit, Hammersmith Hosp., London W12 OHS, England
Adv Radiat Biol; 9:37-73 1981

14. CURRENT CONCEPTS IN ULTRAVIOLET CARCINOGENESIS.

Granstein RD, Sober AJ
(c/o Sober) Dept. Dermatology, Massachusetts General Hosp., Boston, MA, 02114
Proc Soc Exp Biol Med; 170(2):115-125 1982

15. METABOLIC CHANGES AFTER EXPOSURE TO RADIONUCLIDES.

Kalistratova VS
No affiliation given
Med Radiol (Mosk); 27(4):62-71 1982
In RUS

DIETARY FACTORS IN CARCINOGENESIS

16. CAFFEINE: AN UPDATE.

Oser BL, Ford RA
Bernard L. Oser and Associates, 108-18 Queens Blvd., Forest Hills, NY, 11375
Drug Chem Toxicol; 4(4):311-329 1981

17. ANALYSIS OF MUTAGENIC EFFECTS OF FOREIGN SUBSTANCES IN THE FOOD PRODUCTS.

Maganova NB
Inst. Nutrition, Moscow, USSR
Vopr Pitan; (2):3-8 1982
In RUS

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

18. RADIATION EPIDEMIOLOGY (MEETING ABSTRACT)

Marks S
No affiliation given
148th National Meeting of the American Association for the Advancement of Science, January 3-8, 1982, Washington, D.C. American Association for the Advancement of Science 182 pp., 1982.

19. EPIDEMIOLOGICAL STUDIES ON RADIATION CARCINOGENESIS IN HUMAN POPULATIONS FOLLOWING ACUTE EXPOSURE: NUCLEAR EXPLOSIONS AND MEDICAL RADIATION.

Fabrikant JI
Donner Lab., Univ. California, Berkeley, CA, 94720
Yale J Biol Med; 54(6):457-469 1981

20. EPIDEMIOLOGIC APPROACH TO CANCER.

Guinee VF
Dept. Epidemiology, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

21. EPIDEMIOLOGY AND EARLY DETECTION OF CANCER OF THE ESOPHAGUS.

Sorouri P
900 Hillside Road, Wilmington, DE, 19807
Gastrointestinal Cancer 1. Decosse JJand Sherlock P, ed. The Hague, Martinus Nijhoff Publishers, Cancer Treatment and Research, Vol. 3, 452 pp., 1981.

22. METABOLIC EPIDEMIOLOGY OF LARGE BOWEL CANCER.

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23. EPIDEMIOLOGY OF GASTRIC CANCER AND ITS PRECURSOR LESIONS.

Correa P
Louisiana State Univ. Medical Center, New Orleans, LA, 70112
Gastrointestinal Cancer 1. Decosse JJand Sherlock P, ed. The Hague, Martinus Nijhoff Publishers, Cancer Treatment and Research, Vol. 3, 452 pp., 1981.

24. TRENDS IN THE INCIDENCE OF GASTRIC CARCINOMA (MEETING ABSTRACT)

Nobrega FT
Prevention and Internal Medicine, Mayo Clinic, Rochester, MN
Eleventh Annual William Beaumont Gastrointestinal Symposium, March 24-26, 1982, El Paso, Texas. William Beaumont Army Medical Center 56 pp., 1982.

25. CANCER IN INFLAMMATORY BOWEL DISEASE.

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Johns Hopkins Hosp., Baltimore, MD, 21205
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26. GENETIC ASPECTS OF GUT CANCER.

McConnell RB
Broadgreen Hosp., Liverpool, England
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27. HOST AND ENVIRONMENTAL FACTORS ENHANCING CARCINOGENESIS IN THE RESPIRATORY TRACT.

Nettesheim P, Topping DC, Jamasbi R
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Annu Rev Pharmacol Toxicol; 21:133-163 1981

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28. A SEARCH FOR SAFE DRINKING WATER.

Hairsine MA, Schumm HA
Northern Indiana Health Systems Agency, Inc., South Bend, IN
A Search for Safe Drinking Water. Available from National Technical Information Service, Springfield, VA, as HRP-0903845/6:, 68 pp., 1981.

29 OCCUPATIONAL EXPOSURES TO URANIUM: PROCESSES, HAZARDS, AND REGULATIONS.

Stoetzel GA, Fisher DR, McCormack WD, Hoenes GR, Marks S
Battelle Pacific Northwest Lab., Richland, WA
Occupational Exposures to Uranium: Processes, Hazards, and Regulations. Available from National Technical Information Service, Springfield, VA, as PNL-3341-USUR-01:, 91 pp., 1981.

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

30. THE ROLE OF RADIATION AND CHEMICALS IN THE INDUCTION OF MUTATIONS AND EPIGENETIC CHANGES DURING CARCINOGENESIS.

Trosko JE, Chang CC
Dept. Human Development, Coll. Human Medicine, Michigan State Univ., East Lansing, MI, 48824
Adv Radiat Biol; 9:2-36 1981

31. SOME EFFECTS OF CARCINOGENS ON CELL ORGANELLES.

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Dept. Pathology and Oncology, Univ. Kansas Coll. Health Sciences, Kansas City, KS
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

32. CHEMICAL CARCINOGENESIS: INTERACTIONS OF CARCINOGENS WITH NUCLEIC ACIDS.

Rajalakshmi S, Prema M, Sarma D
Dept. Pathology, Univ. Toronto, Toronto, Ontario, Canada
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

33. A MOLECULAR RATIONALE FOR NITROSOUREA INDUCED CYTOTOXICITY.

Tew KD
Lombardi Cancer Center, Div. Medical Oncology, Georgetown Univ., 3800 Reservoir Road, N.W., Washington, DC, 20007
INSERM Symp; 19:61-77 1981

34. MODIFICATION OF DNA AND RNA BASES BY THE NITROSOUREAS.

Ludlum DB, Tong WP
Div. Oncology, Dept. Pharmacology and Experimental Therapy, Albany Medical Coll., Albany, NY, 12208
INSERM Symp; 19:21-31 1981

35. CALMODULIN AND CA2+ IN NORMAL AND TRANSFORMED CELLS.

Veigl ML, Sedwick WD, Vanaman TC
Dept. Microbiology and Immunology, Duke Univ. Medical Center, Durham, NC, 27710
Fed Proc; 41(7):2283-2288 1982

36. METABOLISM AND TOXICITY OF AFLATOXINS.

Hsieh DP, Wong JJ
Dept. Environmental Toxicology, Univ. California, Davis, Davis, CA, 95616
Adv Exp Med Biol; 136(partB):847-863 1982

37. REACTION OF MICROSOMAL AND CYTOSOLIC ENZYMES WITH N-ARYLACETOHYDROXAMIC ACIDS IN THE PRESENCE OF OXYGEN.

Lenk W, Scharmer U
Pharmakologisches Institut, Universitat Munchen, Nussbaumstrasse 26, D-8000 Munchen 2, W. Germany
Adv Exp Med Biol; 136(partB):951-970 1982

38. METABOLIC ACTIVATION AND DEACTIVATION MECHANISMS OF DI-, TRI-, AND TETRACHLOROETHYLENES.

Henschler D, Hoos R

Inst. Toxicology, Univ. Wurzburg, Versbacher Strasse 9, Wurzburg D-8700, W. Germany

Adv Exp Med Biol; 136(partA):659-666 1982

39. METABOLIC ACTIVATION AND HEPATOTOXICITY OF TRICHLOROETHYLENE.

Reynolds ES, Moslen MT

Chemical Pathology Lab., Dept. Pathology, Univ. Texas Medical Branch, Galveston, TX

Adv Exp Med Biol; 136(partA):693-701 1982

40. THE ACTIVATING ROLE OF GLUTATHIONE IN THE MUTAGENICITY OF 1,2-DIBROMOETHANE.

van Bladeren PJ, Breimer DD, Rotteveel-Smijs GM, Hoogeterp JJ, Mohn GR, De Groot A, Van Zeeland AA, Van der Gen A

Dept. Pharmacology, Univ. Leiden, P.O. Box 9502, 2300 RA Leiden, The Netherlands

Adv Exp Med Biol; 136(partA):809-820 1982

41. METABOLISM OF POLYCYCLIC AROMATIC HYDROCARBONS IN PLACENTA.

Juchau MR, Chao ST, Namkung MJ

Dept. Pharmacology, Sch. Medicine, SJ-30, Univ. Washington, Seattle, WA, 98195

Adv Exp Med Biol; 136(partA):555-573 1982

MODIFICATION OF CARCINOGENESIS

42. THE INTESTINAL ENZYMATIC BIOTRANSFORMATION SYSTEM: POTENTIAL ROLE IN PROTECTION FROM COLON CANCER.

Hoensch HP, Hartmann F

Medizinische Universitatsklinik, D-7400 Tubingen, W. Germany

Hepatogastroenterology; 28(4):221-228 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

43. THE ONCOGENIC CIRCLE CLOSES.

Rigby PW

Imperial Coll. Science and Technology, London SW7 2BZ, England

Nature; 297(5866):451-453 1982

44. ANALYSIS OF CASES OF HEPATIC CELL CARCINOMA THAT TRANSFORMED FROM VIRAL HEPATITIS.

Ichida F, Honma A, Soga K

Third Dept. Internal Medicine, Niigata Univ. Sch. Medicine, Niigata, Japan

Nippon Rinsho; 40(2):468-477 1982

In JPN

45. ROLE OF VIRUSES IN THE INDUCTION OF PRIMARY INTRACRANIAL TUMORS.

Walsh JW, Zimmer SG, Perdue ML

Div. Neurosurgery, Univ. Kentucky Medical Center, 800 Rose St., Lexington, KY, 40536

Neurosurgery; 10(5):643-662 1982

METHODOLOGY IN CARCINOGENESIS RESEARCH

46. TRANSLATION OF PHARMACOKINETIC/ BIOCHEMICAL DATA INTO RISK ASSESSMENT.

Dietz FK, Reitz RH, Watanabe PG, Gehring PJ

Toxicology Res. Lab., Health and Environmental Sciences, Dow Chemical, 1803 Building, Midland, MI, 48640

Adv Exp Med Biol; 136(partB):1399-1424 1982

47. IN VITRO ASSAYS FOR THE DIFFERENTIATION OF TUMOR PROMOTORS FROM CARCINOGENS AFTER ROUTINE CARCINOGENESIS BIOASSAYS (MEETING ABSTRACT)

Ward JM, Rice JM

Frederick Cancer Research Center, Frederick, MD

Second Annual Meeting of the Society of Environmental Toxicology and Chemistry, November 22-25, 1981, Arlington, Virginia. Society of Environmental Toxicology and Chemistry 150 pp., 1982.

48. ENVIRONMENTAL CARCINOGENS: SELECTED METHODS OF ANALYSIS. VOLUME 4. SOME AROMATIC AMINES AND AZO DYES IN THE GENERAL AND INDUSTRIAL ENVIRONMENT.

Egan H, Fishbein L, O'Neill IK, Castegnaro M, Bartsch H

Lab. Government Chemist, London, England

IARC Sci Publ (40): 347 pp., 1981.

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MODIFICATION OF CARCINOGENESIS

SERIES CK04 No. 82/12 DECEMBER, 1982

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MODIFICATION OF CARCINOGENESIS BY CHEMICAL AGENTS OR IRRADIATION

1. SINGLE DOSE OF AFLATOXIN B1 RESULTS IN GGT-POSITIVE HEPATIC LESIONS IN SIX WEEKS (MEETING ABSTRACT).

Missibeck N, Boyd J, Campbell TC
Division of Nutritional Sciences, Cornell University, Ithaca, NY, 14853
Fed Proc; 41(3):355 1982

Aflatoxin B1 (AFB1), a potent hepatocarcinogen, is considered so toxic that a single dose large enough to initiate carcinogenesis would kill the animal. A study was undertaken to examine the effect of a single dose of AFB1 on the emergence of gamma-glutamyl transpeptidase (GGT) hepatic foci, an excellent early indicator of hepatocarcinogenesis. Male F-344 rats 28 days of age were fed an AIN-76 diet modified with 1/3 dextrose, 1/3 starch and 1/3 sucrose. Animals were injected ip with 0, 0.05, 0.1, 0.5, 1, 5 and 10 mg/kg AFB1 in dimethylformamide (DMF) at 2.5 mg/kg. All rats given 5 and 10 mg/kg died within 24 hrs. Approx 1/3 of each remaining group died of apparent DMF toxicity within 48 hrs. After 2 wks at least

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10 survivors per group were fed a diet containing 0.05% phenobarbital (PB) to promote the AFB1-initiated lesion. Five animals per group were sacrificed at 6 wks post injection, and livers were examined for GGT-positive foci. Animals receiving 1 mg/kg AFB1 had more lesions than the 0.5 mg/kg AFB1 whereas the 0.1 mg/kg AFB1 animals showed only bile ductular involvement. No foci were observed in the 0.05 mg/kg AFB1 or control rats. In summary, a single dose of AFB1 coupled with the DMF and PB effects resulted in GGT-positive foci as early as six wks after AFB1 injection. (no Refs)

2. EFFECT OF THE DRUGS METHAPYRILENE AND NAFENOPIN ON CARCINOGEN-INDUCED ALTERED FOCI IN RAT LIVER (MEETING ABSTRACT).

Furuya K, Furukawa K, Mori H, Williams GM, Levine W
Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Proc Am Assoc Cancer Res; 23:400 1982

Methapyrilene, an antihistimine and nafenopin, a hypolipidemic agent, have produced liver tumors in rodents, but have shown no evidence of genotoxicity. To determine if these drugs could act as liver tumor promoters, they were fed at 0.05 and 0.1% to F344 rats for up to 24 weeks after the induction of hepatic altered foci by feeding of 0.02% N-2-fluorenylacetamide (FAA) for 8 weeks. The effect of the drugs on FAA-induced altered foci identified by resistance to iron accumulation (IR) and gamma-glutamyl transpeptidase (GGT) activity was compared to that of the liver tumor promoter phenobarbital which enhances the progression of foci to neoplasms. Like phenobarbital, methapyrilene at 0.1% increased the numbers of both IR and GGT-positive foci (6x and 3x respectively) and neoplastic nodules (10x), but not carcinomas, relative to rats returned to the control diet. Nafenopin at 0.1% decreased the numbers of GGT-positive foci by more than 0.3 although IR foci were almost the same as in controls. The number of neoplastic nodules was also reduced by more than 0.5 in the nafenopin group. Thus, methapyrilene like phenobarbital displayed a substantial enhancing effect on hepatocarcinogenesis following FAA while nafenopin was inhibitory. (no Refs)

3. EFFECT OF SELENOSEMICARBAZIDE ON EXPERIMENTAL LIVER CARCINOGENESIS.

Tepliakova GV, Mekhtiev MA, Tagi-Zade SB, Karaeva EM, Alieva NB, Guseinova RA
Res. Inst. Roentgenology, Radiology, and Oncology, Baku, USSR
Eksp Onkol; 4(3):71-73 1982

Effect of selenosemicarbazide (SSC) on liver carcinogenesis was studied in random-bred rats. The rats received the carcinogen thioacetamide (TAA) alone or in combination with the SSC (2 mg/kg, sc). TAA-induced changes in the liver included dystrophy and necrosis during wk 4-8 of the experiment, replacement of liver tissue by connective tissue (wk 10-12), development of cirrhosis and cholangioadenomas (wk 16-20), and formation of malignant cholangiocarcinomas (wk 28). Benign and malignant liver tumors were observed in 95% of the rats exposed to the TAA. SSC administration inhibited, but did not prevent, the development of liver changes. It stimulated hematopoiesis and phagocytosis, enhanced the antiradical activity of liver lipids, and increased the activity of liver lactate dehydrogenase. It did not affect survival of the rats during the first 2-3 mo of the experiment. After 7.5-mo, survival rate in the animals treated with both TAA and SSC was 1.4x greater than that in the animals treated with TAA alone. (15 Refs) (In RUS)

4. INHIBITION OF DEVELOPMENT OF METHYLNITROSOUREA-INDUCED RAT COLONIC TUMORS BY PERORAL ADMINISTRATION OF INDOMETHACIN.

Narisawa T, Sato M, Sano M, Takahashi T
Dept. Surgery, Akita Univ. Sch. Medicine, Hondo 1-1-1, Akita 010, Japan
Gan; 73(3):377-381 1982

The nonsteroid antiinflammatory drug indomethacin, a prostaglandin synthesis inhibitor, inhibited the development of carcinogen-induced large bowel carcinomas in rats. CD-Fischer rats were given carcinogenic pretreatment with intrarectal instillation of 2 mg of methylnitrosourea 3x a wk from the 1st to the 5th wk, in order to produce large bowel tumors. Thereafter, peroral administration of a high or low dose of indomethacin dissolved in drinking water (20 ug or 10 ug indomethacin/ml tap water) for 15 wk was started at the 11th wk, before the tumors developed. At autopsy in the 26th wk just after the completion of the 15-wk treatment, the incidence of developing large bowel tumors was significantly reduced in treated rats, compared to untreated control rats; 17% or 14% vs 67%. However, at autopsy in the 36th wk, 10 wk after cessation of the treatment, the development of tumors in treated rats was significantly increased. Thus, indomethacin inhibited the development of methylnitrosourea-induced large bowel tumors in rats. The effectiveness of peroral administration of indomethacin was comparable to that of intraperitoneal administration. It is postulated that treatment with this drug may effectively prevent the development of large bowel cancer in patients at high risk. (Author abstract) (23 Refs)

5. EFFECTS OF MISCLERONE (CLOFIBRATE) ON DIMETHYLHYDRAZINE-INDUCED INTESTINAL CARCINOGENESIS IN RATS.

Berstein LM, Pozharisski M, Dilman VM
Lab. Endocrinology, Petrov Res. Inst. Oncology, 68 Leningradskaja St., Pesochny-2 Leningrad, USSR
Oncology; 39(5):331-335 1982

Intestinal tumors were induced by treatment with dimethylhydrazine (DMH) (14 mg with reference to base/kg body weight weekly, sc, for 20 wk) in male rats supplied by Rappolovo Animal Farm. Some of the animals received 25 mg/day of misclerone (clofibrate) per os, 5x a wk. Clofibrate treatment did not affect the frequency of tumors of the large and small intestine but was followed by a significant decrease in the number of large- and medium-size tumors. The animals which had received clofibrate beginning from 10 days before the first injection of DMH revealed a relatively greater fraction of exophytic intestinal tumors and less invasion of the intestinal wall, as compared with the animals treated with DMH alone. Possible mechanisms of the effect of clofibrate are discussed. (Author abstract) (33 Refs)

6. MODIFICATION OF PHOTOCARCINOGENESIS BY CHEMICAL AGENTS.

Urbach F, Forbes PD, Davies RE
Center Photobiology, Skin and Cancer Hosp., Temple Univ. Sch. Medicine, Philadelphia, PA, 19140
JNCI; 69(1):229-235 1982

The evidence is long standing and compelling that chemical agents can modify the carcinogenic effects of light. Various types of chemical-light interaction are discussed, and events in chemical photocarcinogenesis, chemically enhanced photocarcinogenesis, and promotion of photocarcinogenesis are

described. Specific examples of each type of process are given, and the importance of interaction of various wavelengths of UV radiation for these processes is stressed. (Author abstract) (15 Refs)

7. ULTRAVIOLET RADIATION SKIN CARCINOGENESIS (MEETING ABSTRACT).

Fry RJ, Ley RD, Grube D
Oak Ridge National Laboratory, Oak Ridge, TN, 37830
Proc Am Assoc Cancer Res; 23:374 1982

Dose-response relationships of UVR-induced skin cancer have been determined in SKH:hairless-1 mice using an unfiltered Westinghouse FS40 sunlamp (280-400 nm). The suitable doses per fraction were determined from investigation on the induction of pyrimidine dimers, erythema and effects on epidermal cell density. Groups of twelve week-old female mice were treated with one of the following regimens: 1) Thirty-six exposures (3/wk for 12 wk) 0, 250, 500, 1000 J/m2, 2) 0, 250, 500, 1000 or 1500 J/m2 followed by 5 ug 12-O-tetradecanoylphorbol-13-acetate (TPA) 3/wk for 52 wk, 3) 500 J/m2 (3/wk for 24 wk) followed by TPA treatment, and 4) 1500 J/m2 3/wk for 1, 3, 6 or 12 wk followed by TPA treatment. Treatment with TPA alone for one yr did not produce carcinomas but did enhance the expression of UVR-induced tumors. For example, the cumulative incidence at 80 wk after 36 exposures to 1000 J/m(2)/exposure was 15% and 54% when TPA was also given. We have observed a curvilinear dose-response for skin cancer incidence in the absence of TPA treatment and a linear, non-threshold dose-response when TPA was used to maximize the expression of tumors. This suggests that initiation events are induced as a linear, non-threshold function of dose. The incidence of cancer was greater, and the latent period shorter, with 72 fractions than after the same total dose given in fewer fractions. (no Refs)

8. PROTECTIVE EFFECTS OF THE HERBICIDE TRIFLURALIN ON BENZO(A)PYRENE INDUCED PULMONARY ADENOCARCINOMA AND FORESTOMACH PAPILLOMAS IN FEMALE A/J MICE (MEETING ABSTRACT).

Triano EA, Lang WR, Kratky MT, Triolo AJ
Departments of Pharmacology and Pathology, Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA, 19107
Fed Proc; 41(3):1548 1982

Mice were fed trifluralin (TF) at 1000, 1500, and 2000 ppm in the diet for 12 or 14 weeks. Tumors were induced by administering 3 mg of benzo(a)pyrene (BP) orally at two time periods. An inhibition of tumorigenesis in lung and forestomach by TF was observed when this herbicide was fed in the diet starting either one week before or one week following exposure to BP. Lung tumors were identified as bronchioloalveolar adenocarcinoma and forestomach tumors as squamous cell papillomas. BP is generally considered to be carcinogenic by virtue of its transformation by microsomal enzymes into chemically reactive intermediates which bind to critical macromolecules of target organs susceptible to tumors. Arylhydrocarbon hydroxylase (BP hydroxylase), a microsomal mixed-function oxygenase, was significantly increased in target (lung and forestomach) and in non-target (glandular stomach) organs when mice were fed TF for a duration of 14 weeks. No significant effects of TF were observed on hepatic enzyme activity. TF was found to decrease the binding of H3-BP to certain liver macromolecules. These findings suggest that various mechanisms resulting from TF treatment may be involved in the observed protection against BP-induced tumors. (no Refs)

9. INHIBITION OF CARCINOGENESIS OF THE RAT MAMMARY GLAND AND MOUSE URINARY BLADDER BY A RETINOID AND AN INDUCER OF INTERFERON SYNTHESIS (MEETING ABSTRACT).

McCormick DL, Becci PJ, Moon RC
Illinois Institute of Technology Research Institute, Chicago, IL, 60616
Proc Am Assoc Cancer Res; 23:354 1982

Retinoids are potent inhibitors of chemical carcinogenesis of the mammary gland and urinary bladder in experimental animals. MVE-2 is a divinyl ether-maleic anhydride copolymer which induces interferon synthesis. These studies were conducted to determine the influence on chemical carcinogenesis of combined administration of MVE-2 and the retinoid N-(4-hydroxyphenyl)retinamide (4-HPR). In the mammary study, virgin female Sprague-Dawley rats received a single iv dose of 20 mg N-methyl-N-nitrosourea per kg body weight. In the bladder study, male C57BL/6 x DBA-2 F1 mice received 8 weekly ig doses of 7.5 mg (4-(butylnitrosoamino)-1-butanol). One week after the final carcinogen treatment, animals in both studies were randomized into groups of 50 as follows: (1) placebo diet (2) 4-HPR, 391 mg/kg diet (3) MVE-2, 25 mg/kg body weight, administered ip in 4 week cycles (3 weeks treatment, 1 week rest) throughout the study (4) MVE-2, 12.5 mg,kg, given as above (5) 4-HPR diet +— 25 mg MVE-2/kg (6) 4-HPR diet + 12.5 mg MVE-2/kg. In both studies, 4 HPR (group 2) and the high dose MVE-2 (group 3) treatments resulted in a significant inhibition of carcinogenesis. The low dose of MVE-2 (group 4) was not active in chemoprevention. No synergistic or additive interaction was observed between 4-HPR and MVE-2 at either dose level. These data suggest that either 4-HPR and MVE-2 inhibit carcinogenesis by a common mechanism, or, more likely, that the compounds have an antagonistic activity which precludes an additive or synergistic interaction in cancer inhibition. (no Refs)

10. INHIBITORY ACTION OF BHA ON CARCINOGENESIS IN F1 AND F2 DESCENDANTS OF MICE EXPOSED TO DMBA DURING PREGNANCY.

Rao AR
Cancer Biology Lab., Sch. Life Sciences, Jawaharlal Nehru Univ., New Delhi - 110 067, India
Int J Cancer; 30(1):121-124 1982

Administration of 500 ug of 7,12-dimethyl benz(a)anthracene (DMBA) to female mice during late pregnancy results in the occurrence of tumors in F1 and F2 generation individuals. F1 progeny had a higher percentage of tumor-bearing individuals than the F2 progeny. All the five litters of F1 females displayed tumor risk but the risk declined progressively in successive litters. Perinatal administration of BHA to the pregnant mice (P generation) receiving 500 ug of DMBA would result in significant reduction in tumor risk among the individuals of F1 generation (p 0.01) and F2 generation (p 0.05). (Author abstract) (43 Refs)

11. MODIFICATION OF N-DIETHYLNITROSAMINE-INDUCED CARCINOGENESIS BY CLONIDINE, CAFFEINE, AND ETHANOL.

Gurkalo VK, Zabezhinskii MA
N. N. Petrov Res. Inst. Oncology, Leningrad, USSR
Eksp Onkol; 4(3):25-29 1982

Roles of adrenergic and cholinergic receptors in the mechanism of chemical carcinogenesis were studied in random-bred male rats. The rats received drinking water containing N-dieth-

ylnitrosamine (DENA: 70 mg/liter) for 4 mo. Rats in Group 1 received DENA alone those in Group 2 received DENA in combination with clonidine (0.05 mg/kg, ip), those in Group 3 received DENA in combination with ethanol (2 ml/rat, po), and those in Group 4 received DENA in combination with caffeine (3.5 mg/kg, sc). The animals were sacrificed 6 mo after initiation of the experiment, and growths of esophageal and liver tumors that were induced were determined. Histological examination of neoplastic changes in the esophagus and liver showed that caffeine stimulated the DENA-induced carcinogenesis, while clonidine and ethanol inhibited the carcinogenesis. Therapeutic administration of clonidine produced marked inhibition of the DENA-induced liver tumors. Changes in acetylcholinesterase activity in the brain during the DENA carcinogenesis indicated that the modifying effects of clonidine, caffeine, and ethanol were associated with stimulation and inhibition of the autonomic nervous system. (25 Refs) (In RUS)

MODIFICATION OF CARCINOGENESIS BY DIETARY COMPONENTS OR DIGESTIVE FACTORS

12. INHIBITORY EFFECT OF A FAT-FREE DIET ON MAMMARY CARCINOGENESIS IN RATS.

Davidson MB, Carroll KK
Dept. Biochemistry, Univ. Western Ontario, London, Ontario, N6A 5C1, Canada
Nutr Cancer; 3(4):207-215 1982

Young female Sprague-Dawley rats were administered 7,12-dimethylbenz(a)anthracene, and a wk later the rats were transferred from commerical feed to a semipurified diet containing 20% corn oil. Eight wk after receiving the carcinogen, half of the rats were changed to a fat-free diet to determine the effects on mammary tumor growth and development. After another 20 wk, rats fed the fat-free diet had significantly fewer tumors per tumor-bearing rat and the tumors were smaller than those of rats that continued on the high-fat diet. Rats fed the fat-free diet weighed somewhat less, but showed no physical evidence of essential fatty acid deficiency. Tumors regressed in about half of the rats on the fat-free diet and in some cases became nonpalpable. After 28 wk on this diet, the remaining rats were transferred back to the high-fat diet and subsequently showed a marked stimulation in tumor growth and development. This continued even after the rats were returned to the fat-free diet 8 wk later, indicating that the tumors were no longer susceptible to the deprivation of dietary fat. The results of this study provide further evidence that dietary fat affects the promotional stage of mammary carcinogenesis. (Author abstract) (23 Refs)

13. EFFECT OF DIETARY FAT AND ANTIOXIDANT ON INCIDENCE OF SPONTANEOUS AND 1,2-DIMETHYLHYDRAZINE-INDUCED TUMORS IN MICE (MEETING ABSTRACT).

Brown RR, Erturk E, Arend RA, Potera C, Remus N, Ruzicka E, Dallmann L
University of Wisconsin Center for Health Sciences, Madison, WI, 53792
Proc Am Assoc Cancer Res; 23:277 1982

In attempts to further define the role of type and quantity of dietary fat and antioxidants on cancer incidence, we studied tumor incidence (spontaneous and dimethylhydrazine (DMH) induced) in mice fed semipurified diets having one of 5 different vegetable fat mixes containing respectively 59% saturated (SAT), 60% monoene (MUF), 59% diene (DUF), 35% transmonoene (TRN), or 4% triene (TUF). Butylatedhydroxyanisole (BHA) was added to some SAT and TUF diets. Weanling CD-1 mice of both sexes (40/group) and female C3H (60/group) were fed these diets having 5% or 17% fat substituted isocalorically for sucrose. Treated mice received 10 weekly subcutaneous injections of 0.25 mg DMH freshly neutralized. Controls received buffer only. DMH caused liver tumors and a few kidney and lung tumors and splenic leukemia, but no colon tumors. More DMH-induced liver and lung tumors were seen in males fed 5% TRN than in other groups but this was not confirmed in males fed 17% TRN. Total tumors in males fed 17% and 5% fats were not different suggesting that when fed isocalorically, the quantity of fat did not influence tumor incidence in CD-1 males. BHA reduced the DMH-liver tumor rate in 17% SAT but not in 17% TUF. DMH-liver tumors were fewer in 17% SAT than in 17% TUF males and this difference was even greater between SAT+BHA+DMH and TUF+BHA+DMH groups. (no Refs)

14. BREAST TUMORS INDUCED BY N-NITROSOMETHYLUREA (NMU) OR DIMETHYLBENZ(A)ANTHRACENE (DMBA) IN CASTRATED MALES: ROLE OF HIGH FAT DIET (MEETING ABSTRACT).

Rivenson A, Silverman J, Weisburger J
American Health Foundation, Valhalla, NY, 10595
Proc Am Assoc Cancer Res; 23:275 1982

We attempted to extend the findings of Fingerhut and Veenema on the induction of prostate cancer in gonadectomized male Fischer F-344 rats on 20% and 5% fat diets, utilizing iv dosing with 7,12-dimethylbenz(a)anthracene (DMBA), and also 2',3-dimethyl-4-aminobiphenyl (DMAB), and N-nitrosome.hylurea (NMU). No prostate cancers were found in rats held for 68 weeks. However, with NMU and DMAB these gonadectomized male rats had breast cancers in a higher incidence on the 20% fat diet with NMU but not with DMAB. All neoplasms were malignant, with invasion and destruction of neighboring tissues, and presenting histologically mixed glandular and squamous structures, quite distinct from lesions usually seen in females. Similar type of adeno-squamous carcinomas could be seen in tumors of the ear duct (Zymbal glands) and bulbo urethral glands developed in rats given the above carcinogens. The topographic location of the tumors labeled grossly as 'breast tumors' excluded other possible similar glandular structures and also a sweat gland tumor since the rat skin does not contain sweat glands. Other tumors noted after the carcinogens given iv were: bladder, DMAB only; small intestine and colon, NMU and DMAB; lung, DMBA, NMU, and DMAB; sc sarcoma, NMU and DMAB; stomach NMU. Several of these cancers exhibited metastases. None of the tumors noted above were present in controls. In summary, NMU and DMAB induced tumors in a number of sites, but selectively caused mammary gland adenocarcinoma and adenosquamous carcinoma, and Zymbal gland adenoepidermoid carcinoma. (1 Ref)

15. EFFECT OF A MARGINALLY LIPOTROPE-DEFICIENT DIET ON METHYLAZOXYMETHANOL ACETATE CARCINOGENESIS.

Kato K, Mori H, Takahashi M, Hirono I
Dept. Pathology, Gifu Univ. Sch. Medicine, Gifu, Japan
Nutr Cancer; 3(4):234-239 1982

The effect of a lipotrope-deficient diet on methylazoxymethanol acetate (MAM acetate) intestinal carcinogenesis was studied in 2 groups of ACI rats. For 10 wk, weanling rats were fed a semisynthetic diet that was either high in fat and marginally deficient in the lipotropes (Group 1), or adequate for rats in all known respects (Group 2). Four wk after the start of the experimental diets, the animals were given a weekly SC injection of MAM acetate, 25 mg/kg body weight, for a total of 5 times. Following the termination of the experimental diets, the animals were fed a basal diet until the end of the experiment (480 days). The tumor incidence in the jejunum-ileum and the number of tumors in the colon were significantly higher in Group 1 than in Group 2. These results suggest that a marginally lipotrope-deficient diet enhances MAM acetate carcinogenesis, probably in its early stage. (Author abstract) (14 Refs)

16. RETINOID INHIBITION OF RADIATION-INDUCED RAT SKIN TUMORS (MEETING ABSTRACT).

Burns FJ, Sargent EV, McCormick D, Albert RE
New York University Institute of Environmental Medicine, New York, NY, 10016
Proc Am Assoc Cancer Res; 23:351 1982

Irradiation of rat skin produces several types of epithelial tumors, including, squamous carcinomas, basal cell carcinomas and a variety of adnexal tumors, each with well-established temporal and dose-response functions. The purpose of the present study was to determine how different exposure schedules to a dietary retinoid affect the yield of tumors induced by ionizing radiation, a direct-acting carcinogen. Male CD-1 rats (Charles River Farms, Wilmington, MA) were irradiated at 28d of age with monoenergetic electrons that penetrated about 1.0 mm into the skin. Retinyl acetate was added to rat lab chow at a concentration of 250 ppm for 20 rats/group as follows: (1) beginning 2 weeks prior to irradiation and ending 1 week after; (2) beginning 1 week after irradiation and continuing indefinitely thereafter; (3) beginning 2 weeks prior to irradiation and continuing indefinitely thereafter. Rats not receiving retinoid began developing tumors about 15 weeks after irradiation and continued to develop tumors reaching about 1.3 tumors/rat at 77 weeks. Neither retinoid treatment schedule 1 or 2 affected the yield of tumors, but schedule 3 reduced the yield of all types of tumors to a level that was indistinguishable from the spontaneous yield in unirradiated non-retinoid treated controls (less than 0.15 tumors/rat). A dietary retinoid when present both during the early and late stages of tumor development produced a powerful inhibitory effect on skin carcinogenesis by ionizing radiation. (no Refs)

17. COMBINED INHIBITORS OF CARCINOGENESIS: EFFECT ON AZOXYMETHANE-INDUCED INTESTINAL CANCER IN RATS.

Nigro ND, Bull AW, Wilson PS, Soullier BK, Alousi MA
Dept. Surgery, Wayne State Univ. Sch. Medicine, 540 East Canfield Ave., Detroit, MI, 48201
JNCI; 69(1):103-107 1982

Outbred male Sprague-Dawley CD rats were fed complete semisynthetic diet and were given supplemental low doses (2 ppm) of selenium as H_2SeO_3 in their drinking water or 50 mg 13-cis-retinoic acid (13-cis-RA) and 2 g beta-sitosterol/kg diet either singly, in combinations of two, or in combinations of all three. Intestinal tumors were induced with eight weekly sc injections of 8 mg azoxymethane (ACM)/kg body weight, and inhibition of tumor formation was determined by tumor counts after 26 weeks. Noncarcinogen controls for each dietary group received eight injections of sterile water. Tumor inhibition was statistically significant in two groups of animals: Dietary control animals had a tumor frequency of 5.07 tumors/rat, rats receiving selenium- plus 13-cis-RA supplementation had a tumor frequency of 3.77, and those being given the combination of all three inhibitors had 2.75 tumors/rat. Analysis of fecal steroids from three AOM groups (dietary controls, the beta-sitosterol plus 13-cis-RA-supplemented group, and the group receiving all 3 additives) after 4 months of supplementation showed that the addition of beta-sitosterol to the diet had no effect on acidic or neutral steroids, regardless of the observed difference in tumor frequency. These results suggest that subpharmacologic doses of inhibitors, particularly those that inhibit the process by different mechanisms, while ineffective alone, may provide significant inhibition of tumorigenesis when used in combination. (Author abstract) (21 Refs)

18. SYNERGISTIC ACTION OF 13-CIS-RETINOIC ACID (CRA) AND 2,6-DIMETHYLNITROSOMORPHOLINE (DMNM) ON THE INDUCTION OF HEPATIC HEMANGIOMAS AND HEMANGIOSARCOMAS IN SYRIAN GOLDEN HAMSTERS (MEETING ABSTRACT).

Stinson SF, Reznik G, Levitt MH
National Cancer Institute, Frederick Cancer Research Facility, Frederick, MD, 21701
Proc Am Assoc Cancer Res; 23:225 1982

During a study designed to test the effect of CRA on the induction of a broad spectrum of neoplasms induced by DMNM, an increase in the incidence of hepatic hemangiomas and hemangiosarcomas was observed in animals given both CRA and DMNM. Groups of 40 male Syrian golden hamsters were given weekly doses of 0, 40, 80 or 160 mg/kg DMNM for 10 weeks. Twenty animals in each group were dosed ig, and the remainder sc. A duplicate series of hamsters was treated in a similar manner except that they were maintained on a diet supplemented with 160 mg/kg CRA. Twelve animals from each group were necropsied at 15, 25, and 40 weeks (six each from ig and sc dosing regimens). Others were killed when moribund. Results by ig and sc routes were comparable. There was no significant difference in time related mortality between hamsters receiving or not receiving CRA, although weight gain was less in those given CRA. There was an increase in the number of hamsters with hepatic hemangiomas or hemangiosarcomas with increasing levels of DMNM except in the 160 mg/kg group which had substantial early mortality due to DMNM toxicity. These neoplasms were observed in 43/120 hamsters given CRA and DMNM but in only 5/120 given DMNM alone. No neoplasms were found in 40 hamsters given CRA alone. These results indicate synergistic action of DMNM and CRA in the induction of hepatic hemangiomas and hemangiosarcomas. (no Refs)

19. INHIBITION OF AFLATOXIN B1 CARCINOGENESIS IN RAINBOW TROUT BY DIETARY BETA-NAPHTHOFLAVONE (BETA-NF), AND INDOLE-3-CARBINOL (I-3-C) (MEETING ABSTRACT).

Hendricks JD, Nixon JE, Bailey GS, Sinnhuber RO
Department of Food Science and Technology, Oregon State University, Corvallis, OR, 97331
Toxicologist; 2(1):102 1982

Several compounds such as flavonoids, selenium, antioxidants and certain vitamins reportedly reduce the induction of cancer in experimental animals, and many function by affecting the mixed-function oxidase (MFO) system. The following compounds: 50 and 500 ppm beta-NF, 1000 ppm flavone, 1000 ppm of a tangeretin-nobilitin mixture, 1000 ppm beta-ionone, 1000 ppm I-3-C and 2000 ppm quercetin were examined for protection against aflatoxin B1 (AFB1) hepatocarcinogenesis and induction of the MFO system in rainbow trout. These compounds were fed to fingerling rainbow trout for 2 months. At that time the activity of several MFO enzymes and cytochrome P450 content were measured and the trout were exposed to 20 ppb AFB1 for 10 days in the same diets. After feeding the test diets without AFB1 for another month and basal diet for 11 months, the tumor incidence was determined. Beta-NF induced the trout MFO system in a dose-dependent manner while tangeretin-nobilitin was less effective. Flavone, quercetin, beta-ionone and I-3-C did not induce the MFO system. I-3-C and beta-NF provided marked protection against AFB1-induced hepatocarcinogenesis, while the other compounds were ineffective. Tumor incidences were 5.1% for 1000 ppm I-3-C, 7.5% for 500 ppm beta-NF and 19.6% for 50 ppm beta-NF, compared to 44.9% for the AFB1-positive control. (no Refs)

20. INHIBITION OF AFLATOXIN-INITIATED PRENEOPLASTIC LIVER LESIONS BY LOW DIETARY PROTEIN.

Appleton BS, Campbell TC
Div. Nutritional Sciences, Cornell Univ., Ithaca, NY
Nutr Cancer; 3(4):200-206 1982

The development of aflatoxin B1-induced hepatic preneoplastic lesions was significantly modified by varying the level of dietary casein fed to animals during the post-dosing period. Using gamma-glutamyl transferase staining to identify areas of cellular alteration, we observed that animals fed a 5% casein diet showed a 75% reduction in lesion development as compared to animals fed a 20% casein diet. Increasing the level of dietary casein from 20% to 40% produced no further increase in response. The results of study, showing an inhibition in the preneoplastic development by a reduction of dietary casein after aflatoxin dosing, suggest that low dietary casein inhibits the promotional phase of the ultimate neoplastic response. (Author abstract) (24 Refs)

21. POTASSIUM INHIBITION OF 1,2-DIMETHYLHYDRAZINE-INDUCED COLON CARCINOGENESIS (MEETING ABSTRACT).

Jacobs MM
Eppley Institute for Research in Cancer, University of Nebraska Medical Center, Omaha, NE, 68105
Proc Am Assoc Cancer Res; 23:345 1982

A reduction in the 1,2-dimethylhydrazine (DMH)-induced colon tumor incidence by potassium in Sprague Dawley (SD) rats is demonstrated. Male SD rats were injected weekly with 20 mg DMH/kg body weight for 20 weeks. Potassium supplemented drinking water was initiated 1 week before the first DMH treatment and was continued until sacrifice 14 weeks after the last DMH treatment. Rats provided 0.5% K (potassium chloride) in the drinking water and Wayne Lab-blox diet were ingesting 2-fold more potassium than the unsupplemented controls. At sacrifice the incidence of DMH-induced colon tumors was significantly reduced to 70% (12/17) with the potassium additive compared to 100% (13/13) in the DMH controls receiving no supplemental potassium. Potassium also reduced the mean diameter of the tumors and appeared to shift the location of the tumors from the proximal to the transverse and distal colon. The predominant extracolonic tumors induced by DMH were ear duct, pancreatic and small intestine. All were reduced by potassium. Survival was better in potassium plus DMH treated rats (85%) than in the DMH only control (65%). At the level tested potassium did not affect the weight gain of the animals. The reduction in colon tumor incidence may be due to potassium inhibition of DMH activation, enhancement of DMH detoxification or to modification of other cellular processes associated with DMH carcinogenesis. (no Refs)

22. EFFECT OF PYRIDOXAL DEFICIENCY ON PANCREATIC DNA DAMAGE AND NODULE INDUCTION BY AZASERINE (MEETING ABSTRACT).

Zurlo J, Roebuck BD, Rutkowski JV, Curphey TJ, Longnecker DS
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Proc Am Assoc Cancer Res; 23:264 1982

The purpose of this study was to determine whether the effects of azaserine on pancreas are pyridoxal-dependent. For DNA damage studies, weanling rats were fed a pyridoxal deficient diet containing 4-deoxypyridoxine, a pyridoxal antagonist, until deficiency was evident (10-12 days). They were then injected with azaserine 90 min before sacrifice. The deficient rats inhibited almost no pancreatic DNA damage (as determined by alkaline elution) in response to azaserine when compared to saline-treated rats on control diet. A structurally different pancreatic carcinogen, N-delta-(N-methyl-N-nitrosocarbamoyl)-L-ornithine, caused DNA damage in both deficient and control groups. Distribution studies with 14C-azaserine showed that the absence of DNA damage was not due to the lack of azaserine transport into the pancreases of deficient animals. In another study, rats were treated with 4-deoxypyridoxine prior to a single azaserine treatment. Rats were killed 4 mo after azaserine administration. There was a significant reduction in the number of atypical acinar cell nodules in antagonist-treated animals compared to controls treated with azaserine but not with the antagonist. These results strongly indicate that azaserine metabolism and carcinogenicity are dependent on pyridoxal. (no Refs)

23. DAUNORUBICIN (D) INDUCED MAMMARY TUMORS IN FEMALE SPRAGUE-DAWLEY RATS AND THE ROLE OF ALPHA-TOCOPHEROL (ALPHAT) AS A MODIFIER TO THE CARCINOGENESIS (MEETING ABSTRACT).

Wang YM, Howell SK, Tsai CC, Van Eys J
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Proc Am Assoc Cancer Res; 23:352 1982

Second malignancies are significant side effects of cancer chemotherapy. Anthracycline antibiotics-induced tumors have been recognized in rats and monkey. We have, recently, investigated the activity of alphaT as a potential modifier to the carcinogenecity-induced by D in female rats. Two groups of rats at age 40 day (less than 125 g) and 48-56 days (150-200 g) re-

spectively were used. In older animals, D (10 mg/kg) injected intravenously induced tumors in 50% (11/22) of the animals. Preinjection with alpha-tocopheryl acetate (alphaTA, 300 mg/kg/day) daily for consecutive 4 days prior to the injection of D reduced significantly the tumor incidence (2/16). In younger animals, tumor incidence was less (5/21) and the pretreatment with the vitamin did not modify the tumor development (9/27). In older animals, organ distribution of 3H-D and 14C-alphaTA changes by each other, however, alphaTA does not alter the concentration of D in mammary tissue and fat. However, in single mammary epithelial cells suspensions isolated in rats after 4 daily treatment of alpha-TA or placebo, the intracellular D distribution was significantly modified in the presence of alphaT and alphaTA. The concentration of 3H-D in nuclear fractions was 30-40% in those cells isolated from alphaT treated animals as compared to the cells from placebo treated animal. It appears the alteration of subcellular D distribution by the vitamin may play a role in the modification of D-induced mammary tumor in rats. (no Refs)

24. SIALIC ACID METABOLISM IN NUTRITIONALLY-MODULATED HEPATOCARCINOGENESIS (MEETING ABSTRACT).

Fox OF, Kishore GS, Graham SA, Carubelli R
Department of Biochemical and Molecular Biology, University Oklahoma Health Science Center, Oklahoma City, OK, 73104
Fed Proc; 41(3):337 1982

The sialic acid content and the activities of the enzymes responsible for the activation, transfer and hydrolysis of sialic acid were investigated in the livers of male Sprague-Dawley rats treated with 2-acetylaminofluorene (AAF). Basal diets containing 20% corn oil, 18% coconut oil + 2% linoleic acid or 2% linoleic acid, with or without supplementation with 0.7% (w/w) butylated hydroxytoluene (BHT) were used. The carcinogenic diets contained 0.05% (w/w) AAF. AAF-treated rats and age-matched controls fed basal diets, were killed after 14-17 weeks of treatment. The livers were used for histological, chemical and enzymological studies. Rats fed high-fat diets showed earlier and higher incidence of AAF-induced hyperplastic nodules (HPN); BHT supplementation greatly retarded the development of these lesions. Increases in sialic acid content and in the levels of CMP (cytosine monophosphate)-sialic acid synthetase and neuraminidase, both cytosolic and particulate, were observed in the livers from AAF-treated rats. Sialyltransferase activity, on the other hand, was not affected. BHT supplementation resulted in lower levels of sialic acid and CMP-NANA synthetase in rats fed low fat and saturated-fat diets; proportional reductions were observed in AAF-treated and in control rats. The chemical and enzymatic changes observed in AAF-treated rats are consistent with an increased turnover of sialoglycoconjugates during the carcinogenic process. (no Refs)

25. EFFECTS OF ARGININE ON THE CARCINOGENICITY OF N-METHYL-N-NITROSOUREA (MNU) AND 7,12-DIMETHYLBENZ(A)ANTHRACENE (DMBA) (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:271 1982

Female Sprague-Dawley rats were used to investigate the effects of dietary arginine on the occurrence of mammary tumors induced by DMBA and MNU. Sixty rats were fed either a control 14% casein diet or the same diet supplemented with 5% arginine starting at 36 days of age. At 50 days of age, 30 rats from each treatment were intubated intragastrically with 7.5 mg DMBA in sesame oil. The remaining 30 in each treatment were given MNU (40 mg/kg body weight) via the jugular vein. Mammary tumors were detected by weekly palpation from 5-18 weeks after carcinogen administration. Dietary arginine supplementation did not alter food intake or weight gain. Total palpable mammary tumors for each group increased at a linear rate. For DMBA-treated rats the rate was 8.1 new palpable tumors per week for controls compared to 4.7 for arginine-supplemented rats. The respective rates were 8.9 and 6.8 tumors/week for MNU-treated rats. In DMBA-treated rats the time for 50% of the rats to develop tumors was increased from 9.3 to 12.5 weeks by dietary arginine supplementation, whereas in MNU-treated rats this time was not affected by arginine. Eighteen weeks after DMBA, 23 control and 21 arginine-supplemented rats had tumors and after MNU the corresponding numbers were 27 and 23. The greater inhibition by arginine of DMBA- than MNU-induced tumor formation indicates that arginine may inhibit the activation of procarcinogens (DMBA). (no Refs)

26. INFLUENCE OF DIET ON THE EFFECTS OF SELENIUM IN THE GENESIS OF MAMMARY TUMORS.

Whanger PD, Schmitz JA, Exon JH
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Nutr Cancer; 3(4):240-248 1982

Two experiments were conducted to study the interaction of various diets with selenium in the genesis of mammary tumors. In the first experiment, virgin C3H mice were fed either an Oregon State University (OSU) chow or this chow plus 0.5 or 2.0 ppm selenium in the drinking water, or Wayne Lab-Blox Chow with or without 2.0 ppm selenium in the water. Selenium significantly reduced the tumor incidence in mice fed the OSU chow, but not in those fed the Wayne chow. In the second experiment, virgin female C3H mice were fed a purified casein-based diet with either lard, butter, corn oil, or rapeseed oil at a 10% level without or with selenium (2 ppm) in the drinking water. Selenium had no significant effect upon tumor incidence in this experiment. Thus, these results indicate that the type of diet has a marked influence on the beneficial effects of selenium in reducing mammary tumors in C3H mice. (Author abstract) (28 Refs)

MODIFICATION OF CARCINOGENESIS BY HORMONAL OR GENETIC FACTORS

27. INHIBITION OF 1,2-DIMETHYLHYDRAZINE INDUCED COLON CANCER IN BALB/C MICE BY DEHYDROEPIANDROSTERONE (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:359 1982

Dehydroepiandrosterone (DHEA) and DHEA-sulfate are major adrenal secretory products in the human with no known biological functions. DHEA is a potent non-competitive inhibitor of mammalian glucose-6-phosphate dehydrogenase, the first enzyme in the pentose-phosphate shunt, a major source of extra-mitochondrial NADPH and ribose-phosphate. Yen et al have reported that long-term treatment of VY-Avy/a mice

with DHEA inhibits weight gain without suppressing appetite, possibly by inhibiting lipogenesis as a result of a reduction in pentose-phosphate shunt activity. The well documented observation that reducing weight gain of laboratory rodents by caloric restriction inhibits many types of tumor formation led us to speculate that DHEA might also have an anti-carcinogenic effect. A single ip injection (10 mg/kg) of DHEA inhibited the tetradecanoylyphorbol acetate (TPA)-stimulation of 3H-thymidine incorporation in mouse epidermis, suggesting that the steroid may inhibit tumor promotion. In current studies 153 weanling Balb/c mice were given mouse chow (controls) and 141 mice received mouse chow containing 0.6% DHEA. All mice were injected weekly with 1,2-dimethylhydrazine (21mg/kg,sc). After 26 weeks of treatment, 10 mice were killed in each group. A mean of 13.2 colon tumors were found in the controls and 2.5 in the DHEA treated. In addition, 26/153 control mice and 0/141 DHEA treated had tumors appearing at the anus. (no Refs)

28. EFFECT OF SEX HORMONES ON THE EXPERIMENTAL INDUCTION OF CANCER IN RAT STOMACH - A PRELIMINARY STUDY.

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Digestion; 23(3):151-155 1982

The effects of sex hormones on the induction of gastric carcinoma by N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) were investigated in Wistar rats. Well-differentiated adenocarcinomas developed with high frequency (88%) on the glandular stomach of male rats given MNNG in drinking water (50 ug/ml) for 4 mo and sacrificed on the 12th mo of the experiment. In female rats given MNNG, no gastric cancer was observed. In the castrated or estradiol-treated male rats, the incidence of carcinoma was lower (29 and 68%, respectively) than in the nontreated male rats. Histologically, poorly differentiated adenocarcinomas were observed more frequently in these groups than in the nontreated male group. In MNNG carcinogenesis, female, castrated male and estrogen-treated male rats had a lower incidence of gastric cancer with lower histological differentiation than did nontreated male rats. (Author abstract) (11 Refs)

29. ESTRADIOL PROMOTION OF NEOPLASTIC LESIONS IN THE RAT VAGINA AFTER INITIATION WITH N-METHYL-N-NITROSOUREA (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:925 1982

Estrogens share a number of biological properties with tumor promoters, and are reported to promote tumorigenesis in two estrogen target organs, the mammary gland and liver. Since the rat vagina is a well described estrogen target organ, we tested the hypothesis that estradiol (E2) is a tumor promoter for the vagina. Rats (CD) ovariectomized at 60 days of age were randomly assigned one week later to one of four treatment groups: 1) initiator only; 2) multiple initiator; 3) initiator-promoter; and 4) promoter only. The initiator was N-methyl-N-nitrosourea (MNU), a short-lived direct acting carcinogen, administered by vaginal instillation in a single dose of 0.25 mg in 75 ul isotonic phosphate buffer to groups 1 and 3. Group 2 received 4 weekly doses of 0.25 mg MNU. Silastic capsules containing E2 (5 mg/ml in 50 ul sesame oil) were implanted in animals of groups 3 and 4, one week after initiator treatment. Silastic implants provided sustained elevated E2 levels, shown by E2 radioimmunoassay and increased uterine weight. After 16 months, vaginal tumor incidence and type were: group 1, 0/9; group 2, 2/8 (papilloma, squamous cell carcinoma); group 3, 4/9 (polyps); group 4, 0/8. Polyps (2-18 mm) were composed of a fibrovascular stroma covered by squamous epithelium of varying thickness. A number of nonneoplastic lesions (groups 3 and 4) were due to E2 with or without MNU. The statistically significant incidence of polyps and their restriction to only the initiator-promoter group suggests that estrogens can promote tumorigenesis in the rat vagina. (no Refs)

30. ESTRADIOL SUPPRESSES 2-AAF HEPATOCARCINOGENESIS IN MALE SPRAGUE DAWLEY RATS (MEETING ABSTRACT).

Griffin MJ
Oklahoma Medical Research Foundation, Oklahoma City, OK, 73104
Proc Am Assoc Cancer Res; 23:919 1982

Twenty-two male Sprague Dawley rats (100 +/-8 gr) were fed a diet containing 0.05% 2-AAF for 16 weeks in an interrupted fashion (3 weeks with 2-AAF, one without). Each day eleven rats received (ip) 0.2 ml of stripped corn oil (CO) while the other eleven received 0.2 ml of oil containing 1 mg of suspended estradiol (ES). The animals, fed ad lib, gained weight over the next 120 days at an average of 0.5 gr/day/rat (ES) versus 1.8 gr/day/rat (CO). After 120 days, the ES treated rats had atrophied testes containing few cells while the CO rats testes appeared normal. At 90 and 120 days, hyperplastic nodules were very prominent in the CO rat livers and this was confirmed by histochemical staining of liver sections for gamma GT. The ES rats had neither gross appearing hyperplastic liver nodules, nor did gamma GT histochemistry indicate nodules. However, a few areas in the ES liver sections stained for gamma GT in a fashion reminiscent of remodeling areas. Microsomal styrene oxide hydrolase activity was induced to 147 +/-16 nmol/min/mg protein in CO livers. ES suppressed this induction to 31 +/-8 nmol/min/mg protein). Preliminary data on tumor incidence at 210 days showed two (of two) CO rats with pathologically certified carcinomas and two ES rats without tumors. The remainder of the rats will be scored for death due to hepatoma. ES may have a direct effect on male rat liver membrane enzyme regulation, since ES has been reported detected in male rat liver endoplasmic reticulum. (no Refs)

31. SUBMANDIBULAR GLAND REMOVAL INCREASES TUMORIGENESIS IN MALE CD-1 MICE (MEETING ABSTRACT).

O'Connell JF, Weiss HS, Pitt JF, Miller RE, Graff DE
Department of Physiology, The Ohio State University, Columbus, OH, 43210
Fed Proc; 41(3):1548 1982

Two wks after surgical removal of the submandibular-sublingual complex, tumors were induced on the shaved back via a two stage system. Initiation was with 0.05mg benzo(a)pyrene in acetone in one wk and promotion by repetitive weekly doses of either 2ug (trial 1) or 4ug (trial 2) of 12-O-tetradecanoylphorbol-13-acetate (TPA). In the first trial mice without the gland complex reached 50% incidence approximately 3 weeks earlier (18 vs 21) and had a 3 times higher rate of increase in the number of tumors per mouse wk than sham operated mice. In the second trial (4ug TPA) mice without the gland complex reached 50% incidence when sham operated and intact controls had 32% and 29% incidence, respectively. There was no

significant change in tissue to appearance of first tumor among treatment groups. Increased tumorigenesis in mice without the gland complex appears unrelated to differences in food consumption or body weight, but might be related to the gland's production of several peptides, including epidermal growth factor. (no Refs)

MODIFICATION OF CARCINOGENESIS BY VIRUSES, BACTERIA OR IMMUNE SYSTEM COMPONENTS

32. EPSTEIN-BARR VIRUS ACTIVATION WITH EUPHORBIACEAE PLANT EXTRACTS: A POSSIBLE CAUSE FOR BURKITT'S LYMPHOMA AND NASOPHARYNGEAL CARCINOMA.

Ito Y, Yanase S, Morigaki T, Kishishita M
Dept. Microbiology, Faculty Medicine, Kyoto Univ., Kyoto 606, Japan
Excerpta Med Int Congr Ser; 571:423-427 1982

Speculation is raised as to whether Epstein-Barr virus-activating substances generated by Fusobacterium and other anaerobes in the mouth, and diterpene esters in Euphorbiaceae extracts with similar activity, might interact in the mouth to initiate the first step of carcinogenesis, which eventually may lead to Burkitt's lymphoma. Similar chronic inflammation in the nasal cavity and nasopharynx could serve to cause nasopharyngeal carcinoma. (2 Refs)

OTHER STUDIES OF THE MODIFICATION OF CARCINOGENESIS

33. RETINOID FEEDING, HORMONE INHIBITION AND/OR IMMUNE STIMULATION AND THE GENESIS OF DMBA-INDUCED RAT MAMMARY TUMORS (MEETING ABSTRACT).

DeHoog JV, Welsch CW
Department of Anatomy, Michigan State University, East Lansing, MI, 48824
Proc Am Assoc Cancer Res; 23:341 1982

Two groups of 320 female Sprague-Dawley rats were treated ig with 20 mg (series I) or 10 mg (series II) of 7,12-dimethylbenzanthracene (DMBA) per rat at 50 days of age. At 53 days of age each series was divided into 8 groups of rats (40 rats/group), ie, (1) controls (C), (2) immunestimulated (IS), (3) hormone inhibited (HI), (4) HI+IS, (5) retinoid fed (RA), (6) RA+IS, (7) RA+HI, (8) RA+HI+IS. HI - Tamoxifen (25 ug/100 g body wt) and 2-Br-alpha-ergocryptine (CB-154) (400 ug/100 g body wt) injected sc once daily. IS - Norcardia rubra (1 mg/rat) injected sc once weekly (series I) or methanol extracted residue (MER) of Bacillus Calmette-Guerin (BCG) (0.5 mg/rat) injected ip at 3 and 5 weeks after DMBA treatment (series II). RA - retinyl acetate, fed daily, 0.2 mM/kg ration (series I) and 0.6 mM/kg ration (series II). Groups 1,2,5 and 6 were sacrificed 12 weeks after DMBA treatment; groups 3,4,7 and 8 at 20 weeks post carcinogen. Mammary tumor incidence was significantly reduced in rats treated with HI or fed a moderate dose of RA. Tumor incidence was further reduced in HI treated rats fed either a moderate or low dose of RA; low dose of RA alone was ineffective. IS alone or in combination did not influence this neoplastic process. (no Refs)

34. EFFECTS OF RAT URINE FRACTIONATED BY MOLECULAR WEIGHT ON URINARY BLADDER CARCINOGENESIS (MEETING ABSTRACT).

Oyasu R, Babaya K, Miyata Y
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Proc Am Assoc Cancer Res; 23:404 1982

The present experiment was conducted to determine whether tumor-enhancing activity exhibited by the whole urine resides in a specific fraction(s) when separated by molecular weight. Normal rat urine after preliminary filtration to remove gross debris was filtered through Amicon Diaflo membranes to obtain two types of filtrate, one at an exclusion level of MW 1,000 and the second at an exclusion level of MW 50,000. These filtrates were tested for tumor-enhancing activity in the heterotopically transplanted rat urinary bladders (HTBs) removed from rats pretreated with the carcinogen N-butyl-N-(4-hydroxybutyl)nitrosamine in drinking water for 4 or 10 weeks. The incidences of cancer in HTBs receiving repeated instillations of the filtrate at MW 50,000 did not differ significantly from those of the HTBs receiving whole urine but were significantly higher than those of the HTBs receiving the filtrate at MW 1,000. In the HTBs which had been exposed to the carcinogen for a longer period of time (10 weeks), the filtrate at MW 1,000, enhanced the bladder tumorigenesis over that of the osmolality control. The results indicate that there may be two classes of tumor-enhancing activity: the first and major one being in the fraction above MW 1,000, and a second one being below MW 1,000. The latter fraction appears to exert its effects only on the cells which are in an advanced stage of carcinogenesis. (no Refs)

35. JEJUNOILEAL BYPASS STIMULATES CELL PROLIFERATION AND ENHANCES EXPERIMENTAL CARCINOGENESIS IN RAT LARGE BOWEL (MEETING ABSTRACT).

Bristol J, Wells M, Williamson R
Department of Surgery, Bristol Royal Infirmary University of Bristol, Bristol BS2 8HW, England
Proc Am Assoc Cancer Res; 23:233 1982

Thousands of small-bowel bypasses have been performed in the management of morbid obesity, but the effects of this procedure on the colon are unknown. We examined the influence of jejunoileal bypass (JIB) on carcionogensis and cell proliferation in the rodent large bowel. Male Sprague-Dawley rats were given either azoxymethane (AOM) 15 mg/kg body weight, or vehicle, by subcutaneous injection weekly for six weeks. One week later, each was subjected to either 85% end-to-side JIB, or sham JIB (jejunal transection, ileotomy, and resuture). At sacrifice 30 weeks postoperatively gut tumors were excised and examined histologically. In vehicle-injected animals colonic length and wet Weight were measured, and the crypt cell production rate (CCPR) was estimated at two sites in the large bowel by counting vincristine-arrested metaphases in individually microdissected crypts. In rats given AOM the median number of large bowel tumors increased from 3 to 8 after JIB. No tumors were found in vehicle-treated animals, but JIB increased colonic length by 19% and wet weight by 29%. CCPR in mid-descending colon was raised from 4.1 +/- 0.8 to 13.7 +/-0.8 cells/crypt/hour, and a similar rise occurred in the transverse colon. JIB enhances experimental large bowel carcinogenesis, probably by stimulating colonic crypt cell proliferation. (no Refs)

36. STUDIES ON THE LEUKEMOGENIC EFFECTS OF IRRADIATION ON FETAL MICE AT VARIOUS STAGES OF EMBRYONAL DEVELOPMENT.

Wang J, Zhou J, Wang Z, Wang S, Deng B, Han Y
Inst. Nuclear Medicine, Chinese Acad. Medical Sciences, Beijing, People's Republic of China
Zhonghua Xueyexue Zazhi; 2(3):141-143 1981

Pregnant mice were irradiated with 60Co (total dose: 250 R) at the implantation (1-5th day), organogenesis (6-12th day) or fetal (13-18th day) period. The tumor and/or leukemia incidences were 21.9%, 11.5% and 36.5%, respectively, as compared to 4.5% of the unirradiated control. The most common types of leukemia observed were lymphocytic, granulocytic and reticulocytic. The highest mortality rate was also observed in mice irradiated during the fetal period. (14 Refs) (In CHI)

STUDIES OF TUMOR PROMOTION OR COCARCINOGENESIS IN MOUSE SKIN

37. EFFECTS OF PEROXIDES ON RODENT SKIN: EPIDERMAL HYPERPLASIA AND TUMOR PROMOTION.

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J Invest Dermatol; 79(1):30-34 1982

Free radical generating peroxides are potent skin irritants. After a single topical application of either 10, 20, or 40 mg of lauroyl peroxide or benzoyl peroxide on the dorsal skin of Sencar mice, the epidermal thickness increased markedly. No major inflammatory or vascular alterations were noted. On the other hand, 15 or 30% hydrogen peroxide produced an extensive epidermolysis, as well as inflammation and vascular injury, followed by quick regeneration and epidermal hyperplasia. Both lauroyl peroxide- and benzoyl peroxide-induced hyperplasias were characterized by a sustained production of dark basal keratinocytes, which constituted approx 10% of the basal cell population during the 1st wk after single topical application. Hydrogen peroxide-induced epidermal hyperplasias also exhibited numerous dark cells, but their presence was less sustained. Although all these peroxides were inactive either as initiators or as complete carcinogens, lauroyl peroxide was as effective as benzoyl peroxide when used as a skin tumor promoter in a two-stage carcinogenesis protocol. In a similar experimental protocol, hydrogen peroxide proved to be a very weak skin tumor promoter. (Author abstract) (16 Refs)

38. DIFFERENTIAL EFFECTS OF RETINOIC ACID AND 7,8-BENZOFLAVONE ON THE INDUCTION OF MOUSE SKIN TUMORS BY THE COMPLETE CARCINOGENESIS PROCESS AND BY THE INITIATION-PROMOTION REGIMEN.

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Cancer Res; 42(9):3519-3525 1982

The present study was designed to elucidate differences in the mechanism of the induction of mouse skin tumors either by the initiation-promotion regimen or by the complete carcinogenesis process. The protocols used to elicit skin tumors were: (a) by the initiation-promotion regimen, a single application of 0.2 umol of 7,12-dimethylbenz[a]anthracene (DMBA) followed by twice-weekly applications of 12-O-tetradecanoylphorbol-13-acetate (TPA); and (b) by the complete carcinogenesis process, a single application of 3.2 umol of DMBA without TPA treatment, or 0.2 umol of DMBA applied once weekly, or 1, 10, 50, or 100 nmol of DMBA applied twice weekly without application of TPA. The biology of tumor formation by the initiation of tumors with a single application of 0.2 umol DMBA followed by twice-weekly applications of TPA differs from tumor induction by once-weekly 0.2-umol doses of DMBA. In the latter case, papillomas developed more slowly and were less common (the tumor induction time was long; tumor yield was less), but carcinomas appeared much earlier. Retinoic acid, a potent inhibitor of tumor promotion by TPA, failed to inhibit and under some experimental conditions significantly (p less than 0.001) enhanced tumor formation by DMBA. Also retinoic acid did not inhibit ornithine decarboxylase induction by DMBA. In contrast, 7,8-benzoflavone, which did not inhibit the induction of ornithine decarboxylase activity by TPA, inhibited the induction of ornithine decarboxylase activity and tumor formation by DMBA. The results indicate that the nature and the mechanism of the biochemical events elicited by the presumed promoting component of carcinogenesis by a complete carcinogen are different from those of the tumor promoter TPA. (Author abstract) (21 Refs)

39. EFFECT OF VITAMIN A AND ANALOGS ON THE INDUCTION OF SQUAMOUS CELL CARCINOMA IN HAIRLESS MICE CAUSED BY SOLAR SIMULATED UV-LIGHT (MEETING ABSTRACT).

Israili ZH, Razdan R, Willis I
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Proc Am Assoc Cancer Res; 23:806 1982

The UV component of the sunlight is the primary stimulus for the majority of skin cancers, the most common of human malignancies. Vitamin A and analogs have been shown to prevent certain chemical carcinogen-induced cancers. We tested the effectiveness of vitamin A and analogs as chemopreventive and/or therapeutic agents in a hairless mouse model in which squamous cell carcinoma in the skin is induced by irradiation with solar stimulating UVA (320-400 nm) plus UVB (290-320 nm) in an escalating dose (9.0-15.3 J/cm2, daily, 5 days/wk for 8 wks). Groups of female mice (12-16 wks old) were irradiated and treated as follows: a) N equals 50, controls, b) N equals 46, all-trans-retinoic acid (t-RA, 20 mg/kg body weight), 8 wks during plus 13 wks post-UV, ie, 21 wks, c) N equals 19, t-RA, 13 wks post-UV, d) N equals 10, 13-cis-retinoic acid (c-RA, 80 mg/kg), for 21 wks, e) N equals 10, c-RA, 13 wks post-UV, f) N equals 10, retinol (33 mg/kg), for 21 wks, and g) N equals 10, beta-carotene (33 mg/kg), for 21 wks. Vitamin A and analogs, as suspensions (in 0.3 ml of 1:1 v/v of Carnation milk:water), were given orally 3 times per wk. Mice were maintained on Purina mouse chow and water ad lib, and were observed for 26 wks. No tumors appeared in unirradiated mice given vitamin A analogs. No significant difference was found in the incidence of cancer (papilloma and tumor) at 26 wk in any of the groups of irradiated animals: a) 20/50, b) 16/43, c) 7/16, d) 3/6, e) 4/9, f) 3/8, and g) 5/8. Retinoyl palmitate (300 mg/kg in 0.2 ml corn oil) given orally, 3 times/wk for 6 wks, to 4 mice with large tumors caused some decrease in tumor size. No histological differences were observed in any of the tumors. (no Refs)

40. TWO-STAGE CARCINOGENESIS ON SKIN AND IN INTERNAL ORGANS OF C57BL/B6 MICE (MEETING ABSTRACT).

Yamasaki H, Cabral JR, Galendo D, Tomatis L
International Agency for Research on Cancer, Lyon, France
Toxicologist; 2(1):63 1982

Promoting effect of phorbol esters, as represented by 12-O-tetradecanoyl phorbol-13-acetate (TPA), has been extensively studied on mouse skin, using a conventional initiation-promotion protocol. Since it has been shown that these tumor promoters exert a variety of biological and biochemical effects on the cells derived from various tissues other than mouse skin, it was of our interest to examine the promoting activity of TPA on internal organs as well as on skin. When fifty C57BL/B6 mice, 6 week old, were painted once with 3 mg of benzo(a)pyrene (B(a)P) and painted with 5 ug of TPA twice a week, 64% of mice developed papillomas by 30 weeks of treatments, whereas none of control groups, treated with B(a)P alone or TPA alone, developed papillomas. These results confirm that C57BL/B6 mice are reasonably sensitive to a conventional two-stage carcinogenesis protocol. However, when the same amount of B(a)P was injected subcutaneously to pregnant mothers and their descendants were painted on skin of the back with 5 ug of TPA twice a week from weaning for 93 weeks, no persistent papilloma was observed. Similarly, the transplacentally exposed mice were injected intraperitoneally with 5 to 10 ug of TPA twice a week. After 100 weeks, the number of mice that died with tumor (4/63) was not significantly different from that in the group without TPA injection (3/64). Taken together, these results suggest that under the experimental conditions used, a conventional mouse skin initiation-promotion carcinogenesis is demonstrable, but transplacental initiation-postnatal promotion of skin and internal organs has not been clearly observed so far in C57BL/B6. (no Refs)

41. 12-O-TETRADECANOYLPHORBOL-13-ACETATE (TPA) AND MEZEREIN-INDUCED ALTERATIONS IN THE SILVER STAINED TWO-DIMENSIONAL GEL PROFILE OF MOUSE EPIDERMAL PROTEINS (MEETING ABSTRACT).

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Proc Am Assoc Cancer Res; 23:381 1982

The two stage model of mouse skin carcinogenesis utilizing the potent tumor promotor TPA or the weak promoter mezerein can be used to study biochemical changes during carcinogenesis in vivo. With two-dimensional gel electrophoresis and silver staining an evaluation of the overall epidermal cell protein pattern at any time after treatment can be made. Eight wk old female CD-1 mice were treated in groups of four with either 0.2 ml acetone or 10 nmoles of TPA or mezerein in 0.2 ml acetone. Six hr after treatment epidermal proteins were extracted and gel electrophoresis performed. Over 200 spots were visualized after silver staining. TPA and mezerein produced similar alterations in the overall protein pattern. Following treatment by either compound several spots showed increased relative intensity of staining compared to the acetone treated controls. These included spots corresponding to proteins of the following approximate molecular weights: 68,000, 66,000, 61,000, 53,000, 52,000, and 37,000 Daltons. No spots were seen that consistently showed decreased relative intensity of staining after treatment. The increase in relative intensity of specific spots is consistent with the known pleiotypic response of mouse epidermis to TPA and mezerein. (no Refs)

42. A STUDY OF PROTEIN MODIFICATIONS INDUCED BY PHORBOL ESTER TUMOR PROMOTERS IN MOUSE SKIN.

Nelson KG
The University of Tennessee, Knoxville, TN
Diss Abstr Int [B]; 42(9):3546-B 1982

The potent tumor promoter TPA (12-O-tetradecanoylphorbol-13-acetate) as well as the weakly promoting hyperplasiogenic agents, mezerein, ethylphenylpropiolate, and mechanical abrasion, induced similar modifications in mouse epidermal proteins particularly among the keratins. Many of the protein changes induced by TPA were associated with its hyperplasiogenic properties. Further evidence which indicated that these protein changes were associated with hyperplasia and not necessarily related to complete promoting ability was obtained by studying the effects of various inhibitors of tumor promotion on the TPA-induced protein modifications. The inhibitors which interfered with the induction of hyperplasia, fluocinolone acetonide and cycloheximide, were found to also interfere with the promoter-induced protein changes. Retinoic acid and tosylphenylalanylcholoromethyl ketone which did not prevent the TPA induced hyperplasia did not significantly influence these protein changes. The keratin polypeptide patterns of papillomas, carcinomas, and epidermis during an initiation-promotion experiment were studied to further understand the role that the keratin modifications play in two-stage carcinogenesis. Distinct keratin patterns were found to be associated with each of these tissues. The TPA-treated epidermis, initiated and non-initiated, contained the same keratin modifications that were observed with one TPA treatment. These keratin changes were also features of all papillomas; however, papillomas could be distinguished from surrounding epidermis by the presence of considerable charge heterogeneity among the high molecular weight keratins. The most striking protein alterations observed in the carcinomas was a significant reduction in the high molecular weight keratins. In fact, the carcinoma keratin profiles were very similar to those patterns observed in the basal cells isolated from adult epidermis following a single treatment with a hyperplasiogenic agent. (no Refs)

CELL CULTURE STUDIES OF MECHANISMS OF MODIFICATION

43. RESPONSES OF PRENEOPLASTIC EPIDERMAL CELLS TO TUMOR PROMOTERS AND GROWTH FACTORS: USE OF PROMOTER-RESISTANT VARIANTS FOR MECHANISM STUDIES.

Colburn NH, Wendel E, Srinivas L
Lab. Viral Carcinogenesis, NCI, Frederick, MD, 21701
J Cell Biochem; 18(3):261-270 1982

The mechanism of late stage promotion was studied in the JB6 mouse epidermal cell line. Second-stage promoters, including phorbol diesters which act both as first- and second-stage promoters, and mezerein, which acts primarily as a second-stage promoter, showed activity in promotion of transformation in JB6 cells. The second-stage antipromoter retinoic acid inhibited promotion of transformation by 12-O-tetradecanoylphorbol-13-acetate (TPA) but the antiproteases antipain and leupeptin, which inhibit first-stage promotion, did not, even at concentrations greater or equal to those that inhibited promotion of transformation in 10T1/2 cells. Three of four mitogen-

resistant lines, R219, R6141, and R23, were promotable to anchorage independence by TPA. Thus, promotion of transformation by TPA in JB6 cells can occur without the release-from-quiescence of mitogenic response to TPA. Cross-resistance to mezerein and epidermal growth factor (EGF) occurred in two TPA promotion-resistant clones of JB6, C130, and C125. C125 and C130 showed moderate to high levels of EGF binding while three promotable lines, R219, R6141, and R23, showed little or no EGF binding. Thus, EGF binding is not a requirement for promotion of transformation in JB6 cells by TPA. The role of TPA-induced changes in the sialic-acid-containing plasma membrane glycolipids was investigated. TPA produced a 10-fold decrease in precursor incorporation into a trisialoganglioside and a 2-fold increase in incorporation into an unidentified ganglioside. These findings suggest that gangliosides may be important in promotion of tumor cell phenotype. A model for the sequence of events necessary for promotion of transformation in JB6 cells is proposed. (32 Refs)

44. EFFECTS OF 12-O-TETRADECANOYLPHORBOL-13-ACETATE ON FIBROBLASTS FROM INDIVIDUALS GENETICALLY PREDISPOSED TO CANCER.

Antecol MH, Mukherjee BB
Dept. Biology, Center for Human Genetics, McGill Univ., Montreal, Quebec, H3A 1B1, Canada
Cancer Res; 42(9):3870-3879 1982

The purpose of the present study was to determine whether skin fibroblasts from individuals, either with an inherited predisposition to cancer or with genetic disorders usually associated with a high risk of cancer, can be oncogenically transformed in vitro by a tumor promoter alone. The effects of chronic and limited applications of 12-O-tetradecanoylphorbol-13-acetate (TPA) on several properties that are associated with transformation were examined using skin fibroblasts from individuals with polyposis coli, a familial cancer syndrome, xeroderma pigmentosum, Fanconi's anemia, and trisomy 21. The results of this study show that TPA treatment induces similar changes on cellular morphology, growth rate, saturation density, epidermal growth factor binding, and cytoskeleton in fibroblasts from both normal and genetically predisposed individuals. None of these cell lines, however, acquired anchorage-independent growth or unlimited growth potential in culture after chronic application of TPA. These observations suggest clearly that skin fibroblasts from individuals with either a genetic predisposition to or a high risk of cancer may not exist in a preneoplastic or 'initiated' state susceptible to oncogenic transformation by TPA alone and that the mechanism of genetically determined cancer induction may be different from that of chemical carcinogenesis. (Author abstract) (28 Refs)

45. GENERAL PROCESS OF INDUCTION OF SQUAMOUS METAPLASIA BY CYCLIC ADENINE NUCLEOTIDE AND PROSTAGLANDINS: MOUSE PROSTATE GLANDS.

Schaefer FV, Custer RP, Sorof S
(c/o Sorof) Inst. Cancer Res., Fox Chase Cancer Center, 7701 Burholme Ave., Philadelphia, PA, 19111
Cancer Res; 42(9):3682-3687 1982

Squamous metaplasia is a common abnormality of cellular development and differentiation in the epithelia of many organs, including the prostate gland in humans. Agents known to elevate the level of intracellular cyclic adenine nucleotide have been found to direct various kinds of epithelial cells onto a pathway of epidermoid (squamous) development and a differentiation marked by keratin production. We report here that the mixture of the cyclic adenine nucleotide; N6,O2'-dibutyryladenosine cyclic 3':5'-monophosphate (0.1 mM); prostaglandins E1, E2, and B1 (each 5 ug/ml); and papaverine (1 uM) induces extensive squamous metaplasia and keratin production in the epithelial cells of mouse ventral prostate glands cultured for 3 wk. The components of the mixture act synergistically. A 10-fold higher concentration of N6,O2'dibutyryladenosine cyclic 3':5'-monophosphate (1 mM) alone is as effective as is the mixture. The presence of either the retinoid, retinylidene dimedone, or the phorbol ester, phorbol-12,13-didecanoate, at 1 uM completely prevents the induction of squamous metaplasia. The results suggest that cyclic adenine nucleotide and indirectly prostaglandins E1 and E2 may play important roles in the spontaneous and exogenously induced production of squamous metaplasia. These same inducing agents have also been found in other studies to bring about squamous metaplasia and keratinization in culture in the mammary glands of mice and the breast tissue of humans, as well as to accelerate normal epidermization in chick embryo skin. The findings in prostate gland, mammary glands, and skin derived from embryonic or adult animals and humans, spanning three species and two classes of vertebrates, suggest that cyclic adenine nucleotide augmented by prostaglandins E1 and E2 may act generally on diverse types of epithelia to bring about normal and metaplastic squamous cell development and a differentiation marked by keratin production. (Author abstract) (50 Refs)

46. THE INFLUENCE OF ASBESTOS ON THE FORMATION AND REMOVAL OF BENZO(A)PYRENE-DNA ADDUCTS IN A HAMSTER TRACHEAL EPITHELIAL CELL LINE (MEETING ABSTRACT).

Eastman A, Mossman BT, Bresnick E
Department of Biochemistry and Pathology, University of Vermont College of Medicine, Burlington, VT, 05405
Proc Am Assoc Cancer Res; 23:236 1982

The effect of asbestos fibers (crocidolite and chrysotile) on the interaction of benzo(a)pyrene (BP) with a hamster tracheal epithelial cell line (HTE-B) has been investigated. When BP alone was incubated with HTE-B cells, 50% of the applied hydrocarbon was recovered as water soluble metabolites at 8 hr while 5% was recovered as intracellular unmetabolized BP. After 8 hr incubation with BP, the medium was replaced and a 50% reduction in alkylation was observed in 24 hr with about 80% removed by 5 days. High performance liquid chromatography separation of the DNA adducts demonstrated six adducts. Of these six adducts, two were rapidly removed while two were relatively poorly removed during the 5 day repair period. In comparative studies, BP was coated onto asbestos and applied to HTE-B cells. An enhanced uptake was observed with 80% BP associated with the cells after 1 hr. Metabolism was only slightly inhibited as compared to experiments without asbestos but at 8 hr nearly 50% of the applied hydrocarbon was retained by the cells in unmetabolized form. Analysis of repair was complicated by continued formation of alkylated products in DNA after removal of BP. However, after 24 hr post-treatment, only 5% of the applied BP remained in the cells. At 5 days, it appeared that removal of DNA-bound adducts was inhibited. Experiments with both crocidolite and chrysotile gave the same results. It is concluded that the cocarcinogenic effect of asbestos may be due to enhanced cellular uptake of BP as well as inhibition of subsequent DNA repair. (no Refs)

47. A PROBABLE MECHANISM FOR SYNERGISTIC EFFECT IN CHRYSOTILE AND BAP INDUCED TRANSFORMATION (MEETING ABSTRACT).

Chang MJ, Singh NP, Hart RW
National Center for Toxicological Research, Jefferson, AR, 72079
Proc Am Assoc Cancer Res; 23:199 1982

It is generally believed that the initial step of chemically induced cellular transformation is the fixation of DNA damage(s). Using a normal human skin fibroblast cell culture system, we investigated: 1) the cytotoxic effect of chrysotile asbestos; 2) thymidine incorporation, and 3) cellular uptake of BaP (benzo(a)pyrene) under the influence of asbestos. We observed: 1) chrysotile asbestos (10 ug/ml) exerted cytotoxicity at a cell density below confluency; 2) chrysotile treatment enhanced thymidine incorporation from the first to the fourth day post-treatment both in the presence or absence of BaP; 3) BaP uptake was enhanced in the culture simultaneously treated with asbestos. The preliminary findings indicate that protein and RNA binding of BaP was enhanced in the presence of chrysotile asbestos. Based on the data collected, we suggest that in the event of co-exposure of chrysotile asbestos and BaP, more DNA damage will result, that thymidine incorporation will be enhanced and is indicative of increased levels of DNA replication thereby leading to the fixation of genetic damage. (no Refs)

48. DIFFERENTIAL CELL CYCLE PHASE SPECIFICITY FOR NEOPLASTIC TRANSFORMATION AND MUTATION TO OUABAIN RESISTANCE INDUCED BY N-METHYL-N'-NITRO-N-NITROSOGUANIDINE IN SYNCHRONIZED C3H10T1/2 CL8 CELLS.

McCormick PJ, Bertram JS
Dept. Experimental Therapeutics, Grace Cancer Drug Center, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Proc Natl Acad Sci USA; 79(14,part1):4342-4346 1982

The transformable mouse embryo fibroblast cell line C3H10T1/2 Cl8 has been employed to study the induction by the carcinogen N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) of morphological transformation and mutation to ouabain resistance throughout the cell cycle. Cells were synchronized by means of isoleucine deprivation for 24 hr and initiated DNA synthesis with a high degree of synchrony 7.5 hr after release of the isoleucine block. At various intervals throughout the cell cycle cultures were treated with MNNG at 1.0 ug/ml and the induction of cytotoxicity, morphological transformation, and ouabain-resistant colonies was determined. All three phenomena exhibited marked cell-cycle phase dependency. Maximal induction of transformation occurred in cultures treated 7.5 hr after release from isoleucine deprivation, when the cells were at the G1/S boundary. In contrast, induction of ouabain-resistant colonies was at a minimum at the time of maximal induction of transformation, and peak induction of ouabain resistance did not occur until 16-18 hr after release from the isoleucine block, when cells were in late S phase. A close correlation was observed between the induction of cytotoxicity and of ouabain-resistant mutants. The results suggest that differences exist in the production or cellular processing of the various early lesions. (Author abstract) (41 Refs)

REVIEWS AND OTHER RELATED STUDIES

49. BIOLOGICAL CARCINOGENESIS.

Rich MA, Furmanski F
AMC Cancer Res. Center and Hosp., Lakewood, CO
Biological Carcinogenesis. New York, Marcel Dekker, Inc., 310 pp., 1982.

The general principles which govern carcinogenesis are identified for each of the major classes of carcinogens and the extent these principles are applicable to the carcinogenic process induced by other classes of agents is determined. Current knowledge on the interaction of carcinogens and the identification of biological systems where viral, chemical, and physical carcinogens are demonstrably interactive are described. Mechanisms in viral carcinogenesis are discussed with respect to: T-cell growth, T-cell growth factor, T-cell leukemias and lymphomas and isolation of a new type-C retrovirus, properties of sarcoma growth factors produced by sarcoma virus transformed cells, and interactions of murine leukemia viruses with hematopoietic stem cells. Mechanisms in chemical carcinogenesis are discussed with respect to activation of carcinogenic polycyclic hydrocarbons by metabolism, involvement of a protein kinase in multistage skin tumor promotion, and the effect of tumor-causing chemicals on the control of mutagenesis and differentiation in mammalian cells. Transformation of cloned mammary epithelial cells following combined treatment with mouse mammary tumor virus and dimethylbenz(a)anthracene, virus-cell interactions during hormonal carcinogenesis, and separate pathways for viral and chemical carcinogenesis in the mouse mammary gland are described. A molecular approach to studies of chemical carcinogen-virus interaction is presented. Other presentations deal with multistage recombinational origin of leukemogenic viruses, radiation-induced leukemogenesis, neoplastic transformation of cultured cells by herpes simplex virus type 2 and carcinogens, modulation of adenovirus transformation and replication, and transformation of murine fibroblasts. (682 Refs)

50. ALCOHOL AND CARCINOGENESIS.

Seitz HK, Czygan P, Kommerell B
Schwerpunkt Gastroenterologie, Medizinische Universitatsklinik, Bergheimer Str. 58, D-6900 Heidelberg 1, W. Germany
Leber Magen Darm; 12(3):95-107 1982

The relationship between alcoholism and carcinogenesis is reviewed. Alcohol has been linked to increased incidences of cancers of the oropharynx, larynx, esophagus, liver, and probably the pancreas and rectum. Beverages with high alcohol content present greater risks than wine or beer. Alcoholism has a synergistic effect on carcinogenesis caused by smoking. Cirrhosis of the liver caused by alcoholism is important as a precancerous condition. Beer consumption increases the risk of pancreatic cancer; chronic pancreatitis is not involved as an intermediate stage. Beer consumption also increases the incidence of rectal cancer. Other cancers possibly related to alcohol abuse include carcinomas of the kidney, prostate, bladder, breast, and thyroid. Animal studies indicate that alcohol by itself is not carcinogenic. Alcohol apparently has a cocarcinogenic effect. Alcohol may induce specific enzyme systems that interact with carcinogens. It may be active in either the initiation phase, the promotion phase, or both. In the gastrointestinal tract it may induce carcinogenesis by local effects. Systemic effects include alterations in hormonal and immune functions, as well as in the actions of vitamins and minerals. In addition, alcoholic beverages contain a number of carcinogenic substances. (179 Refs) (In GER)

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As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. ASBESTOS CARCINOGENESIS: ASBESTOS INTERACTIONS AND EPITHELIAL LESIONS IN CULTURED HUMAN TRACHEOBRONCHIAL TISSUES AND CELLS.
Haugen A, Harris C
Div. Cancer Cause and Prevention, NCI, Bethesda, MD
Recent Results Cancer Res; 82:32-42 1982

2. REVIEW: ORAL CONTRACEPTIVES AND MENOPAUSAL ESTROGENS IN RELATION TO BREAST NEOPLASIA.
Brzezinski A, Schenker JG
Dept. Obstetrics and Gynecology, Hadassah Univ. Hosp., POB 12000, 91120 Jerusalem, Israel
Isr J Med Sci; 18(4):433-438 1982

3. LIVER DISEASES DUE TO HORMONAL CONTRACEPTIVES.
Lie TS
Chirurgische Klinik und Poliklinik, Universitat, Sigmund-Freud-Str. 25, D-5300 Bonn 1, W. Germany
MMW; 124(20):489-494 1982
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RADIATION CARCINOGENESIS

4. THE WORK OF THE NRPB 1977/80 AND A REVIEW OF THE FIRST 10 YEARS.
National Radiological Protection Board
Natl. Radiological Protection Board, Chilton, Didcot, Oxfordshire OX11 0RQ, England
The Work of the NRPB 1977/80 and a Review of the First 10 Years. Chilton, Didcot, Oxfordshire, National Radiological Protection Board, 70 pp., 1981.

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5. ALCOHOL AND CARCINOGENESIS.
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6. ZINC, COPPER, AND MANGANESE IN IMMUNE FUNCTION AND EXPERIMENTAL ONCOGENESIS.
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7. TRENDS IN CANCER INCIDENCE: CAUSES AND PRACTICAL IMPLICATIONS. PROCEEDINGS OF A SYMPOSIUM HELD OSLO, NORWAY, 6-7 AUGUST 1980.
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ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

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9. NASAL CARCINOMA IN WOODWORKERS: A REVIEW.
Wills JH
Sch. Medicine, Uniformed Services Univ. Health Sciences, 4301 Jones Bridge Road, Bethesda, MD, 20814
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12. INHALATION CARCINOGENESIS: AN OVERVIEW.
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13. THE NITROSAMINE HAZARD.
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